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FACULDADE DE MEDICINA

Thiago Dias Fernandes

Estudo do Reflexo Trigêmino-Facial em pacientes com Apneia do Sono

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor em Bases Gerais da Cirurgia.

Orientador: Prof. Titular Luiz Antonio de Lima Resende

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1. Apneia Obstrutiva do Sono. 2. Reflexos. 3. Nervo facial. 4. Eletrofisiologia.

Palavras-chave: Apneia Obstrutiva do Sono; Blink Reflex; Reflexo Trigêmino-Facial.

Dedicatória

*Dedico este trabalho à minha esposa - **Paula**, que esteve ao meu lado, amparando e incentivando de maneira única e fundamental. Ao meu filho - **Lucas**, meu motivo maior para seguir em frente. Aos meus pais - **Marcos e Vania,** e ao meu irmão - **Gabriel**, que formaram meu alicerce e apoiaram minha jornada.*

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Albert Einstein

Resumo da Tese

Introdução: O reflexo trigêmino-facial (RTF) pode ser estudado e mensurado através de técnica eletrofisiológica - o *Blink Reflex.* As respostas R2 são integradas em nível ponto-bulbar por neurônios que têm relação anatômica e funcional com a formação reticular, por sua vez relacionada à fisiologia do sono e fisiopatologia da Síndrome da Apneia Obstrutiva do Sono (SAOS).

Objetivo: Estudar o RTF em pacientes com SAOS e correlacionar os achados com parâmetros polissonográficos.

Métodos: Foram estudados 50 pacientes adultos com SAOS, de ambos os sexos, submetidos à polissonografia, estudos de condução nervosa sensitiva e motora nos membros, e estudo do RTF.

Resultados: Dos 50 pacientes estudados, 10 preencheram critérios de exclusão. Dentre 40 pacientes analisados, o RTF foi normal em 7, mostrou achados de hiperexcitabilidade em 16 (grande amplitude, longa duração e/ou curta latência) - *Grupo 1*, e achados de hipoexcitabilidade em 17 (baixa amplitude e/ou latência prolongada ou resposta ausente) - *Grupo 2*, com diferenças estatisticamente significativas entre os grupos ($p < 0.0001$). As alterações do RTF não apresentaram correlações estatisticamente significativas com os diferentes parâmetros polissonográficos estudados.

Conclusões: A avaliação eletrofisiológica do RTF permitiu separar pacientes com SAOS em 3 grupos (normal, achados de hiperexcitabilidade, achados de hipoexcitabilidade) evidenciando normalidade, disfunção e/ou lesão de grupos neuronais do tronco encefálico.

Palavras-Chave: Reflexo Trigêmino-Facial, Apneia Obstrutiva do Sono, Blink Reflex

Abstract

Background: The Blink Reflex can be evaluated through electrophysiological method. The R2 late responses are mediated by neuronal groups in the pons and medulla with anatomical and physiological relation with the reticular formation, wich is related to sleep physiology and physiopathology of the Obstructive Sleep Apnea (OSA).

Objective: To study the Blink Reflex in patients with OSA and to correlate the findings with polysomnographic parameters.

Methods: Fifty adult patients with OSA diagnosis were enrolled for polysomnography, limb conduction studies and Blink Reflex.

Results: Ten patients fulfilled exclusion criteria. From 40 patients studied, 7 showed normal Blink Reflex, 16 hyperexcitability findings (high amplitude, long duration, and/or short latency response) - *Group 1*, and 17 hypo excitability findings (low amplitude and/or prolonged latency, or absent response) - *Group 2*, with significant differences between groups ($p < 0.0001$). No statistically significant difference was observed between the Blink Reflex abnormalities and the polysomnographic parameters evaluated.

Conclusion: The electrophysiological evaluation of the blink reflex afforded to distinguish OSA patients in 3 groups (normal, hyperexcitability findings, hypo excitability findings) related to normality, dysfunction and/or injury of neuronal groups in the brainstem.

Keywords: Blink Reflex, Obstructive Sleep Apnea

Sumário

Blink Reflex Study in Patients with Obstructive Sleep Apnea

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Abstract

Introduction: The objective of this study has been to demonstrate Blink Reflex abnormalities in patients with Obstructive Sleep Apnea (OSA) and to correlate the findings with polysomnographic parameters.

Methods: Fifty adult patients with OSA diagnosis were enrolled for polysomnography, limb conduction studies and Blink Reflex. The patients were grouped according to the Blink Reflex abnormalities. We proposed a numeric scale to quantify the Blink Reflex abnormalities for statistical analysis.

Results: Ten patients fulfilled exclusion criteria. From 40 patients studied, 7 showed normal Blink Reflex, 16 hyperexcitability findings (high amplitude, long duration, and/or short latency response) - *Group 1*, and 17 hypo excitability findings (low amplitude and/or prolonged latency, or absent response) - *Group 2*, with significant differences between groups ($p < 0.0001$). No statistically significant difference was observed between the Blink Reflex abnormalities and the polysomnographic parameters evaluated.

Conclusion: The electrophysiological evaluation of the blink reflex afforded to distinguish OSA patients in 3 groups (normal, hyperexcitability findings, hypo excitability findings) related to normality and probably dysfunction and/or injury of neuronal groups in the brainstem.

Keywords: Blink Reflex, Obstructive Sleep Apnea

Introduction

Obstructive sleep apnea (OSA), first described in 1965 by two different groups, Jung & Kuhlo, and Gastaut, is a common medical condition with increasing recognition[1]. Nowadays it is well known as an independent risk factor for cardiovascular disease, neurocognitive impairment and a cause of decreased health-related quality of life[2,3,4].

Epidemiological data vary because of methodological heterogeneity among studies. Most of the studies estimate prevalence between 2 and 4% in general population, however it can reach 32,8%. It can be influenced by gender, age, weight and other intrinsic factors of each population[5,6,7,8,9,10].

OSA is defined by clinical symptoms and signs (daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, snoring) in the presence of five or more respiratory events (apneas, hypopneas, respiratory effort related arousals - RERA) per hour of sleep or at least 15 obstructive events per hour of sleep in the absence of sleep related symptoms and signs[11].

The OSA pathogenesis is complex and multifactorial. It includes individual pharyngeal anatomical characteristics, inadequate pharyngeal dilator muscle activation and unstable ventilatory control[3,12]. The consequences may result in the typical clinical picture, secondary damage to muscles and nerves because of trauma and inflammation due to vibration during snoring and to neuronal malfunctioning or even loss[3]. Chronic intermittent hypoxia is the hallmark of OSA and it may negatively affect the central neuronal network underlying breathing control, like the pre-Bötzinger, Bötzinger complex and other neuronal structures in the brainstem, mainly in the ventrolateral medulla[12,13].

Electromyographic techniques for studying the blink reflex were first used by Kugelberg in 1952[14]. From then on, this test was widely applied for research and clinical investigation of disorders of the brainstem, trigeminal and facial nerves[15,16,17,18,19,20,21,22,23].

In this study, the blink reflex was undertaken in patients with OSA in order to determine possible electrophysiological abnormalities, its localization in the brainstem and correlation with polysomnographic parameters.

Methods

After approval by the Ethics Committee on Human Research of our Institution, from January 2012 to December 2014 50 patients aged 18-75 years that filled the criteria of the American Academy of Sleep Medicine for OSA were studied. All patients were consented before enrollment for overnight polysomnography (PSG), conduction nerve studies and blink reflex.

Exclusion criteria

The exclusion criteria were diabetes, alcoholism, chronic renal failure, connective tissue diseases, previous exposure to toxic environmental agents, polyneuropathy (previous known or diagnosed by conduction studies), medical history of cranial nerve palsies, neoplasms, head trauma, stroke, movement disorders, epilepsy and use of drugs affecting central nervous system.

PSG

Standard overnight PSG was performed using 24-Channel *Meditron Sommeil 840* equipment and software *Somnium Series 800* with the following recordings: electroencephalography (6 channels), electro-oculograms (2 channels), submental electromyogram (3 channels), limbs electromyogram (2 channels), electrocardiography (2 channels), piezo-electric belt for thoracic movement recording, piezo-electric belt for abdominal movement recording, motion sensor for body position recording, thermistor for inspiratory/expiratory flow recording, nasal cannula based pressure, accelerometer for vibration recording in the neck and a finger pulse oximeter. Polysomnongrams were scored manually following the American Academy of Sleep Medicine guidelines. The polysomnographic findings evaluated for the purposes of this study were, Arousal Index (AI), Respiratory Disturbance Index (RDI), Time of Hypoxia (SatO2 < 92%). OSA severity were defined as mild for RDI ≥ 5 and < 15, moderate for RDI ≥ 15 and < 30, and severe for RDI ≥ 30, according to the American Academy of Sleep Medicine (AASM) diagnostic criteria[8].

Blink Reflex

The studies were conducted in a semi-darkened room with subjects in dorsal decubitus position. Surface disc electrodes were placed G1 over the orbicularis oculi muscle, 1 cm below the lateral epicantal point and G2 2 cm behind the lateral epicantal point. This positioning was used for both Channel 1 and 2. The ground electrode was positioned over the chin. Stimulations were performed with the cathode over the supraorbital foramen with pulse square waves of 0.2 ms duration and 20mA intensity. At least 10 seconds interval between stimulations were adopted to avoid habituation. Filter band-pass was set to 20-3000 Hz, sensibility to 200 μV/division, and analysis time to 10 ms/division[24,25]. A MEB-9400 Nihon-Kohden Neuropack S1 apparatus was used in all examinations.

Analysis

Normative data previously obtained in our laboratory were used, as follows ($\bar{X}$+3SD): R1 superior limit of the latency = 13.0 ms; R2 superior limit of the latency = 40 ms; R2 superior limit of the amplitude = 400 μV; R2 superior limit for duration = 60 ms.

Patients were grouped according the Blink Reflex findings:

Normal Group;

Group 1 - Hyperexcitability findings (high amplitude, long duration, and/or short latency response);

Group 2 - Hypo excitability findings (low amplitude and/or prolonged latency, or absent response);

After grouping, the PSG data were paired and submitted to statistical analysis.

Statistical Analysis

For statistical analysis, we proposed a numerical scale value of the blink reflex as every R1 alteration, 1 point; elongated R2 duration, 2 points; increased amplitude, 3 points; decreased R2 amplitude and duration, 4 points.

The score values of the blink reflex for the Groups 1 and 2 were analyzed

by the non-paired Student “t” test. The test for mean comparison used gamma distribution. The different values of the polysomnographic parameters and the numeric score values of the blink reflex were analyzed by the Pearson correlation coefficient.

Results

From 50 patients, 10 fulfilled exclusion criteria. Eighteen female patients (mean age 54,27 years) and 22 male patients (mean age 56,54 years) were included (N=40).

Thirty-three patients (82,5%) had abnormal blink reflex and seven had normal findings (Examples in Figure 1). In this group, 4 were female, the mean age was 57,57 years and 4 patients were classified as mild OSA, 2 as moderate and 1 as severe OSA.

Sixteen patients met the criteria for hyperexcitability, six of them female. The mean age was 53,56 years, and 5 patients were classified as mild OSA, 8 as moderate, 3 as severe. Figure 2 exemplifies these abnormalities.

Seventeen patients showed hypo excitability findings (Group 2), 8 were female. The mean age of the group was 56,52 years and six patients were classified as mild OSA, 5 as moderate, 6 as severe. The abnormalities are showed in the Figure 3.

The comparison for the numeric scale values of the blink reflex between Groups 1 and 2 by the non-paired Student “t” test showed significance ($p<0.0001$). Gamma distribution was used for the comparison between means because of the asymmetrical data. It showed for AI, $p = 0.92$; for N3 $p = 0.73$; for AI/N3 = 0.14; for RDI $p = 0.15$; for O2 saturation $p = 0.43$ (Table 1). No significant difference was observed.

The Pearson correlation coefficient for the Group 1 showed positive correlation between AI and RDI ($r = 0.69$; $p = 0.0032$); positive correlation between AI/N3 ratio and O2 saturation ($r = 0.58$; $p = 0.0179$); positive correlation between RDI and O2 saturation ($r = 0.65$; $p = 0.0066$).

For the Group 2, it was observed negative correlation between AI and N3

(r = - 0.49; p = 0.0460); positive correlation between AI and RDI (r = 0.75; p = 0.0006); negative correlation between N3 and RDI (r = - 0.64; p = 0.0052). AI/N3 positive correlation with O2 saturation (r = 0.60; p = 0.0109). Positive correlation between RDI and O2 saturation (r = 0.80; p < 0.0001).

No correlation between the OSA parameters and numeric scale of the blink reflex for the 2 groups was observed.

Discussion

The search for a biomarker of central nerve system lesion or morbidity due to OSA or for others disorders is a frequent theme in medical research[26,27,28,29,30].

Our first studies about the electroencephalogram (EEG) in uremia showed improvement of the background activity after dialysis or renal transplantation, suggesting that the EEG abnormalities caused by chronic renal failure may be reversible. Even the triphasic waves with great amplitude, frequently seen in the uremic coma, may be reversible some hours or days after they have appeared[31].

In 2002 our research group found that in the end-stage-renal disease patients undergoing hemodialysis, blink reflex abnormalities were predominantly seen in patients with longer dialysis time. Different types of late R2 component abnormalities were recorded, probably caused by functional or anatomical impairment of the low brainstem reticular formation[32].

In another study, great amplitude and long duration R2 responses recorded in patients with chronic renal failure could be reversible, however, persisting R2 responses with low amplitude and short duration were related to poor prognosis. This type of abnormality was preferentially seen in uremic patients that died some months after the study[33].

The blink reflex is a neurophysiologic technique that brings information about functions integrated in, or mediated by the brainstem, mainly the R2 component, a response that involves a polysynaptic pathway in the pons and lateral medulla[34,35,36,37].

The Bötzinger complex, pre-Bötzinger complex and other neuronal circuitry responsible for the respiratory control during sleep, are located bilaterally

in the pons and in ventrolateral medullary reticular formation, in close anatomic relation to the neural structures that generate the blink reflex responses. Although the location of neural control for the respiratory drive to upper airway motoneurons is not well established, some studies propose that the hypoglossal, trigeminal and facial motor nuclei are involved[38].

The blink reflex observed in our patients with OSA syndrome have several similarities with that observed in chronic uremia, as reversible great amplitude and/or long duration R2 component, or persistent low amplitude, short duration R2 response, observed in both clinical conditions. These findings suggest a dysfunction of the integration site of the reflex once both trigeminal and facial nerves were not affected.

In this study, we also presented a proposal to quantitative blink reflex assessment through a scale ranging from 0 (normal) to 18 points (maximum of abnormalities) for statistical analysis. The comparison of the numeric scale of the blink reflex between Groups 1 and 2 by the non-paired "t" test showed $p<0.0001$. Our results indicate that the blink reflex may be usefull for the classification of patients with OSA in 3 Groups: normal, hyperexcitability pattern and hypoexcitability pattern. Normal blink reflex was preferentially seen in patients with mild OSA, however studies with a larger sample size should be performed to confirm this observation.

Statistical analysis for correlation of the different polisomnographic parameters and the scale by the mean correlation test showed no significance between groups 1 and 2.

Analysis by the Pearson correlation coefficient between polisomnographic parameters showed significance in both groups, and these results for the OSA were all expected (direct relation between AI and RDI, minutes with saturation below 92% and RDI, inverse relation between AI and N3)[39,40].

The literature about neurophisiological brainstem studies in patients with OAS is scarce, however, our conclusions are in accordance with Gadoth, 1988[41,42,43]. The blink reflex can be a tool in the evaluation of brainstem

dysfunction in patient with OSA and probably, the hypoexcitability findings are related to the most severe grades of the disease.

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Table 1. Data comparison between Groups 1 and 2.

	Group 1		Group 2		
Variable	Mean	StdDev	Mean	StdDev	p-value
BLINK Score	9.13	2.68	16.29	2.17	<0.0001
N3	10.09	7.95	9.03	7.75	0.7260
AI	29.48	12.40	29.1	12.23	0.9196
AI/N3	8.03	13.74	15.95	22.92	0.1453
Sat min	51.63	67.57	74.94	78.62	0.4334
RDI	23.45	17.70	35.03	34.82	0.1467

AI = Arousal Index, RDI = Respiratory Disturbance Index.

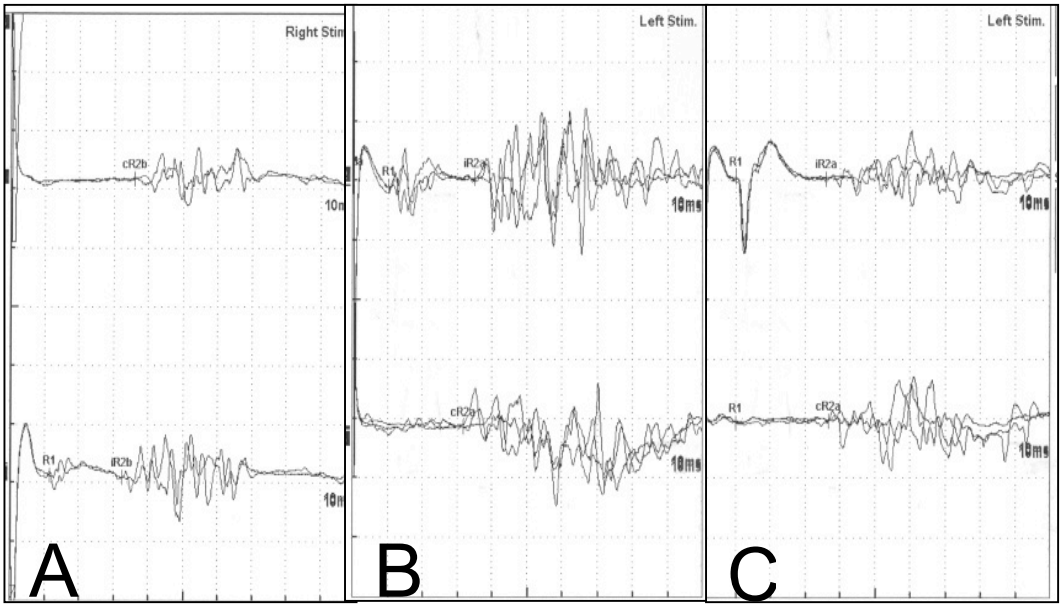

Figure 1 - Examples of normal blink reflex obtained in our Laboratory (10ms/div; 200uV/div). R1 response usually begin at 10-12 mSec, with normal amplitude and morphology variability (maximum of 300 uV). The R-2 responses duration usually variates from 40 to 60 mSec , also with normal amplitude and morphology variability (maximum of 420uV). A, B and C, right, left and left stimulus, respectively.

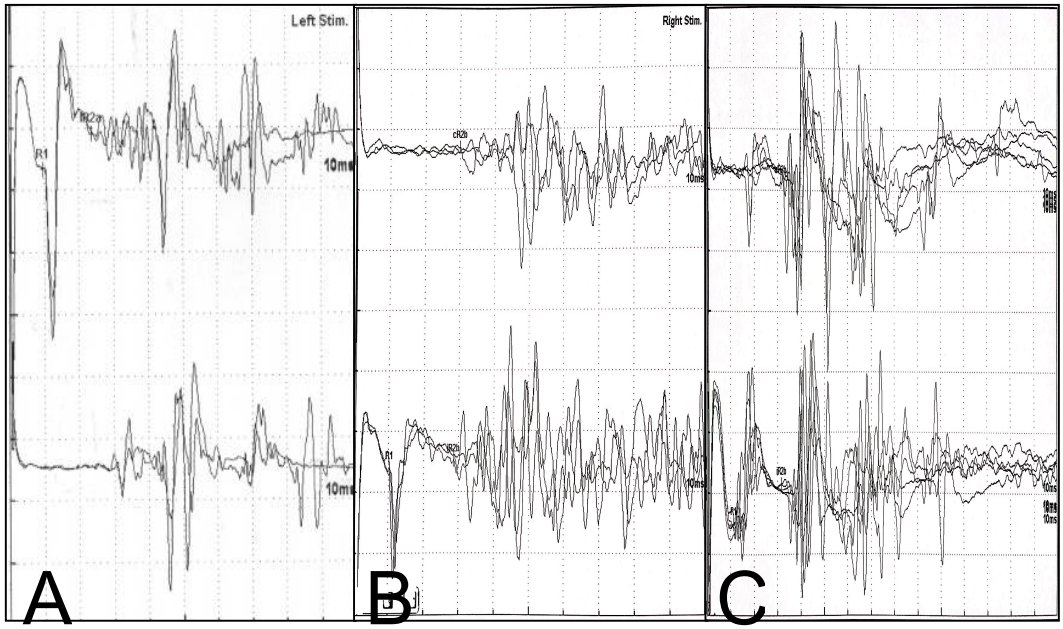

Figure 2 - Examples of abnormal blink reflex obtained from the patients of the Group 1 (10ms/div; 200uV/div). A – Left stimulus. Giant R1 response (1 mV),). The ipsilateral R2 response begin at the final segment of R1 at 15 – 20 mSec, as an extension of R1, the duration is elongated (more than 70 mSec). B – Right stimulus. The R1 amplitude is greater then our normative data (300uV). High amplitude and long duration of ipsilateral R2 response. The R2 contralateral response is normal. C - Right stimulus. Polyphasic R1 response, increased amplitude and abnormal morphology of R2 ipsilateral and contralateral R2 responses. An abnormal smaller contralateral R1 response is also present. This is the only patient who died months after this study.

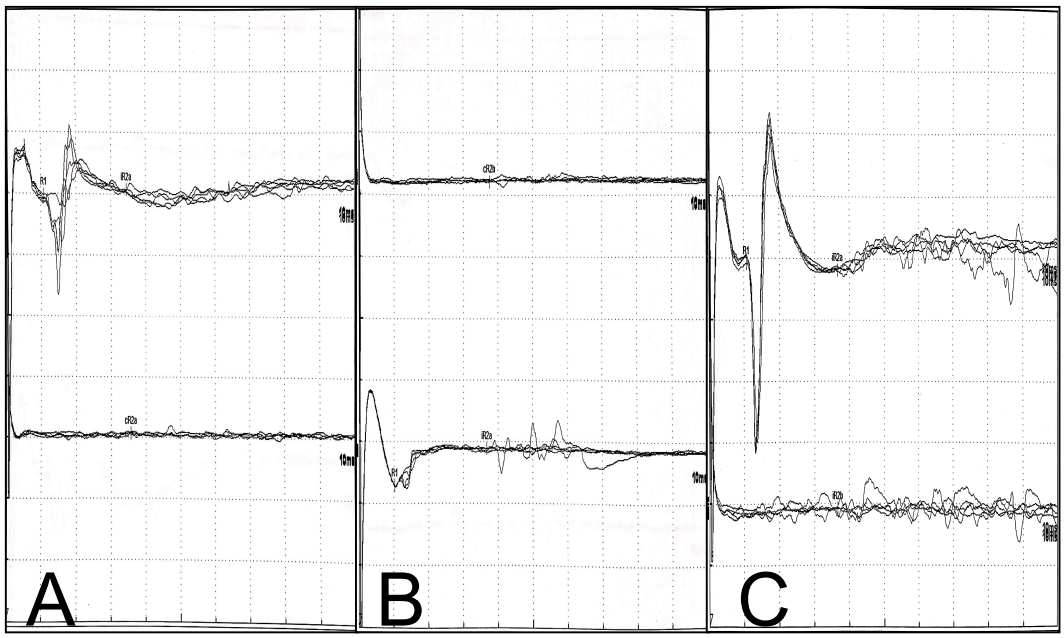

Figure 3 - Examples of abnormal blink reflex obtained from the patients of the Group 2 (10ms/div; 200uV/div). **A** – The left stimulus evoked normal R1 response but R-2 are bilaterally absent. **B** – The right stimulus evoked small R-1 response, the ipsilateral R-2 is minimal, the contralateral R-2 is absent. **C** – Atypical finding, giant R-1 response in a patient with hipo excitability of the R-2 responses. In **A** and **C** the amplitudes of the R1 responses assure the absence of technical problems.

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO DO REFLEXO TRIGÊMINO-FACIAL EM PACIENTES COM APNEIA DO
Pesquisador: Thiago Dias Fernandes
Área Temática:
Versão: 1
CAAE: 21319213.7.0000.5411
Instituição Proponente: Departamento Neurologia,Psicologia e Psiquiatria
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 417.848
Data da Relatoria: 07/10/2013

Apresentação do Projeto:
A Síndrome da Apneia do Sono (SAS) ¿ é caracterizada pela repetitiva parada da respiração durante o sono e suas consequências durante o dia, que incluem sonolência diurna excessiva, fadiga, redução da função cognitiva. Existem 3 tipos, baseados em causas diferentes¿ . A Síndrome da Apneia Obstrutiva do Sono (SAOS), a Síndrome da Apneia Central (SAC) e a Apneia Mista . A literatura mostra que 1 entre 5 adultos tem SAOS leve e 1 entre 15, moderada ou grave e que existe associação com sexo masculino e obesidade .

A Síndrome da Apneia do Sono é doença ¿com fisiopatologia multifatorial envolvendo anatomia do aparelho respiratório, regulação de tônus muscular de vias aéreas superiores pela substância reticular ativadora ascendente, limiar intrínseco de despertar e anormalidades de controle do ritmo ventilatório. O reflexo trigêmino-facial elicitado por estímulo elétrico (Blink reflex) é método eletrofisiológico simples, acessível, reprodutível e que avalia neurônios internunciais bulbo-pontinos¿.

O presente estudo tem por hipótese: que pacientes com Síndrome da Apneia do Sono têm alterações no reflexo trigêmino-facial.

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Método:
Trata-se de estudo transversal, descritivo, como objetivo de pós-graduação ¿ mestrado.

O estudo será realizado com pacientes de 18 a 65 anos, de ambos os sexos, com diagnóstico de SAOS, SAC ou Apneia Mista, de graus variáveis, atendidos no Ambulatório de Distúrbios do Sono e que serão encaminhados ao Laboratório de Eletroneuromiografia para estudos de condução nervosa e pesquisa do Blink reflex.
Segundo o pesquisador ¿O Blink reflex é método simples, acessível, facilmente reprodutível e que avalia neurônios internunciais bulbo-pontinos¿.

Serão realizados dois tipos de exames:

1- A condução sensitiva e nervosa motora nos membros superiores
Condução nervosa sensitiva do nervo mediano por técnica antidrômica. Eletrodos captadores posicionados nas pregas interfalângicas; catodo distal do estimulador posicionado em marca cutânea feita a caneta, com terra interposto.

No caso de pacientes com hipótese de poli neuropatia periférica durante os estudos de condução dos membros superiores, ainda que excluídos do estudo, terão exame eletroneuromiográfico realizado também em membros inferiores, para documentação da doença.

2- Blink reflex
Exame com estímulo elétrico no supercílio,
Eletrodos G1 posicionados 1,0 cm abaixo do epicanto lateral dos olhos; Eletrodos G2 2,0 cm posteriores ao epicanto lateral dos olhos; catodo distal do estimulador posicionado sobre ramo supra-orbital do trigêmeo esquerdo, terra sobre a testa.

Critério de Inclusão:
Pacientes com Síndrome da Apneia do Sono, entre 18 e 65 anos, de ambos os sexos.
Critério de Exclusão:
Diabetes, alcoolismo, doenças sistêmicas que alteram nervos periféricos como insuficiência renal, distúrbios endócrinos e colagenoses, história de exposição ocupacional a agentes tóxicos e

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ambientais, polineuropatia periférica de qualquer etiologia, outras doenças neuromusculares, neoplasias, traumatismos crânio-encefálicos prévios, doenças neurológicas prévias como acidentes vasculares encefálicos, distúrbios do movimento, dentre outras; antecedentes de paralisias de nervos cranianos, quaisquer anormalidades nos estudos de condução nervosa sensitiva e/ou motora, detectadas em qualquer membro.

Objetivo da Pesquisa:
Descrever respostas do reflexo trigêmino-facial em pacientes com síndrome da apneia do sono

Avaliação dos Riscos e Benefícios:
Riscos:
Desconforto transitório secundário ao estímulo elétrico.
Benefícios:
Possível correlação futura com prognóstico.

Comentários e Considerações sobre a Pesquisa:
O projeto está bem redigido e estruturado, apresentando detalhamento metodológico de todos os procedimentos.

O projeto apresenta todos os procedimentos e análises a serem realizadas.

Consta cronograma e todos os documentos necessários estão anexados ao projeto.

Orçamento de R$ 2.000,00

O projeto não precisa ser enviado à CONEP

Considerações sobre os Termos de apresentação obrigatória:
O TCLE está redigido de forma clara e relata que o exame com aplicação de estímulo elétrico no supercílio pode causar desconforto.

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Recomendações:
Mencionar no TCLE que todos os procedimentos poderão causar desconfortos.

Conclusões ou Pendências e Lista de Inadequações:
Não hápendências, somente a sugestão de que no TCLE conste que todosos procedimentos poderão causar desconfortos

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:
Projeto de Pesquisa aprovado em reunião do CEP de 07 de outubro de 2.013, sem necessidade de envio à CONEP.

Ao Final deste projeto os pesquisadores devem encaminhar ao CEP o respectivo Relatório Final de Atividades.

BOTUCATU, 08 de Outubro de 2013

Assinador por:
Trajano Sardenberg
(Coordenador)

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