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Research Article

Association Between Functional Neurometry Test Results, Blood Biomarkers Indicative of Subclinical Inflammation and the Increase in Slow Waves Observed in the Quantitative EEG of Patients with Attention Deficit and Hyperactivity Disorder (ADHD)

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Abstract

Background: There are findings demonstrating the association between the functional neurometry-FN exam and blood biomarkers.

Objective: The association between FN-exam, biomarkers indicating subclinical inflammation and amplitude of Delta (2 - 4 Hz) and Theta (4 - 8 Hz) in ADHD was evaluated.

Method: FN-assessments, blood tests and quantitative EEG (QEEG) were performed. The groups were: control = 32 and ADHD = 61. FN investigated: anxiety control-AC [Expected value ≥ 75%], Baroreflex index-BRI [≥ 90%], hemodynamics-HD [≤ 10%] and physiological response-PR [31.5º to 32.5º]. The biomarkers were: total leukocytes-TL, ferritin, C-reactive protein-CRP, fibrinogen, 25-hydroxy-vitamin-D3, IgE, expressed in frequencies and percentages, analyzed by the chi-square, and by the Mann-Whitney QEEG. All results were expressed as Median (Minimum-Maximum), p ≤ 0.05*.

Results: The ADHD presented: AC = 37.12 (9.00 - 75.18), BRI = 87.28 (67.33 - 93.66), HD = 17.66 (12.11 - 32.50) and PR = 26.10 (21.00 - 29.00) with the highest frequencies of the biomarkers: TL > 6000 [44/61, (81.19%)], eosinophils > 7: [54/61, (88.52%)], neutrophils > 55: [40/61, (65.57%)], 25-hydroxyvitamin-D3 < 40 [47/61, (77.04%)] and IgE > 200 [20/61, (32.78%)], compared to controls: AC = 80.44 (68.00 - 85.00); BRI = 92.00 (88.00 - 95.00); HD = 9.00 (08.00 - 10.00); PR = 32.00 (31.00 - 32.50); TL > 6000 [12/32, (37.50%)], eosinophils > 7: [7/32, (21.87%)], neutrophils > 55: [9/32, (28.12%)], 25-hydroxyvitamin-D3 < 40 [11/32, (34.37%)] and IgE > 200 [3/32, (9.37%)]. There was an increase in the amplitudes of delta (F7 = 19u, F3 = 16.90u, Fp1 = 20.20u, Fz = 18.50u, Fp2 = 20.10u, F4 = 16.80u and F8 = 18.80u) and theta (F7 = 27.7u, F3 = 29.3u, Fp1 = 26.5u, Fz = 29, 7u, Fp2 = 23.7u, F4 = 29.7u and F8 = 26.7u) in the ADHD, compared to the respective controls (F7 = 10.90u, F3 = 11.10u, Fp1 = 10.30u, Fz = 9.25u, Fp2 = 13u, F4 = 9.95u and F8 = 10.10u) and (F7 = 22.65u, F3 = 23.45u, Fp1 = 23.55u, Fz = 24.5u, Fp2 = 22, 1u, F4 = 23.55u and F8 = 22u).

Conclusion: The functional neurometry exam indicated low anxiety control and functional oxygen in patients with ADHD due to adrenal insufficiency and/or liver overload, low baroreflex index, hemodynamics with reduced blood flow velocity and/or low temperature in the proximal annular phalanx, indicating possible food incompatibility. Subclinical inflammation caused by allergenic and inflammatory foods was also observed and, finally, high amplitudes of delta and theta waves were observed in patients with ADHD, which seems to indicate a consequence of subclinical inflammation and low functional oxygen at the mitochondrial level of the brain. Thus, the NF test, blood biomarkers indicative of subclinical inflammation, and high results of delta and theta brain wave amplitudes, when associated with the clinic, can help in the diagnosis and treatment of ADHD.

Keywords: *Functional Neurometry; Biomarkers; Subclinical Inflammation; QEEG; ADHD*

Abbreviations

AC: Anxiety Control; BRI: Baroreflex Index; HD: Hemodynamics; PR: Physiological Response; EM: Expected Minimum; ER: Expected Range; Med (Min-Max): Median/(Minimum-Maximum); RVI: Reference Value for Inflammation; TL: Total Leukocytes; Eo: Eosinophils; N: Neutrophils; SF: Serum Ferritin; CRP: C-Reactive Protein; Fb: Fibrinogen; VD3: 25-Hydroxy-Vitamin D3; IgE: Immunoglobulin E

Introduction

School complaints of inattention and hyperactivity reach a percentage of 25% of people, reaching up to 7% of school-age children, similarly, worldwide [1]. Up to 60% of patients diagnosed in childhood continue to have symptoms into adulthood [2]. Diagnosis in male patients is 3 to 4 times more frequent than in female patients [1].

In ADHD, symptoms of attention deficit, impulsivity and hyperactivity and other abnormalities are commonly analyzed in the functional context, involving: hormonal changes [3], noradrenergic neurotransmitters [4], GABA and glutamate imbalance [5], serotonergic [6] and dopaminergic [7] and brain wave imbalances [8].

Studies of the patterns observed in the quantitative EEG in the literature are more prominent in the Theta/Beta ratio [6], where the algorithm that interconnects the computer to the amplifier calculates the total Theta waves (4 - 7 Hz) and compares to total Beta waves (15 - 23 Hz). The expected result of this relationship so that no association is found with the patterns of brain electrical activities found in ADHD is between 1.2 and 2. When the value of this theta/beta ratio is above 2, it indicates an excess of slow waves of the Theta type (4 - 7 Hz), when compared to the total of fast waves of the beta type (15 - 23 Hz) [9].

There seems to be a correlation between this increase in slow waves in the brain of people who also have a subclinical inflammation that starts in the intestine, overall, with food sensitivity, especially to gluten [10], with the activation of zonulin in the presence of gliadin [11], inhibiting occludin, releasing the opening of tight junctions that allow the increase of intestinal villi, generating hyper permeability that can be perpetuated by the constant presence of various inflammatory cytokines [12].

There are already findings in the literature demonstrating the relationship between the gut and the brain [13,14], especially in the context of subclinical inflammation caused by food hypersensitivity [15]. However, the literature still seems to be very scarce when it comes to studies that demonstrate an association between food and the quality of energy generation represented in brain electrical activity, especially in individuals with food incompatibility (food intolerance, allergy, or hypersensitivity).

Thus, this study aims to associate the results of the Functional Neurometry exam, Blood biomarkers indicating subclinical inflammation and slow brainwave amplitude, Delta (2 - 4 Hz) and Theta (4 - 7 Hz).

Aim of the Study

The objective of this study was to evaluate the association between the functional neurometry test, biomarkers indicating subclinical inflammation and delta (2 - 4 Hz) and theta (4 - 8 Hz) amplitude in patients with ADHD.

Materials and Methods

Ninety-three (93) male patients aged between 8 and 21 years were selected. The subjects were divided into 2 groups: a) Group of patients with medical statements attesting they do not have ADHD (Control, n = 32); and b) Group of patients with a medical diagnosis of ADHD (ADHD, n = 61). The evaluation was performed in the double-blind category (neither the patient nor the person who performed the evaluation knew about the patient's medical diagnosis. The accomplishment of this research complied with the ethical precepts of Resolution 466/12 or 510/16 of the National Health Council, was submitted to the Ethics and Research Committee of the Federal University of Pernambuco (UFPE) through the Brazil Ethics Platform with the number CAAE: 46873421.4.0000.5208 and at the end of the process it was approved with opinion No. 4.884.253.

The groups thus formed were evaluated in three stages:

1. **1st step:** Assessment through functional neurometry to investigate signs of food incompatibility. This exam lasts between 06 and 10 minutes, on average, individually. The result comes out after the exam is carried out.
2. **2nd step:** Assessment of the pattern of brain electrical activity compatible with attention deficit hyperactivity disorder (ADHD) through quantitative EEG in each patient. This exam lasts 40 minutes, on average, individually. The result comes out after the exam is carried out.
3. **3rd step:** Evaluation of the following biomarkers: blood count, serum ferritin, C-reactive protein, fibrinogen, vitamin D3 and IgE.

All patients were evaluated at the Instituto do Cérebro de Pernambuco (ICerPE). Functional neurometry and quantitative EEG tests were performed in an air-conditioned room at a temperature of 19º ± 2ºC. The equipment and sensors of this method, already registered with the National Health Surveillance Agency (ANVISA), are periodically updated/calibrated, enabling the functional assessment of the autonomic nervous system (ANS), neurophysiological signs and brain mapping/neuroimaging, under Reg. ANVISA nº 81403519002 [16].

After the evaluations with functional neurometry of each patient, the physician of the team delivered to each patient a blood test request already funded by the first author of this study.

Eligibility criteria: Inclusion: patients who reported not practicing physical activity frequently, did not use supplements and had no nutritional monitoring were included. Exclusion: patients who used glucose control, cholesterol and controlled drugs were excluded.

Specification of assessment instruments

Functional neurometry

Functional neurometry is method that was organized by the author Nelson Alves Pereira Júnior to perform an analysis established in 3 (three) positions: Dorsal decubitus; stand-up and orthostatic (DLO), called DLO Analysis, structured in 6 categories, called: I) Anxiety control; II) Cardiac variability, III) Baroreflex index; IV) Hemodynamics; V) Physiological response and VI) Brain neurometry [16].

In this study, only 4 categories were evaluated using the Neurometry method: 1) Anxiety control, 2) Baroreflex index, 3) Hemodynamics and 4) Physiological response. In the first category of this study, called anxiety control, the non-cognitive response (not voluntarily controlled in a rational way) is measured, that is, it is the ANS response [17]. The author uses galvanic skin response sensors (dermal conductance) [18]. These sensors apply a very small and imperceptible electrical voltage to the skin, specifically, on the volar surface of the index and middle fingers, where there are numerous sweat glands, allowing the measurement of electrical current impedance in microohm units [16].

The second category, baroreflex index, concerns the functioning of baroceptors [19]. The more the baroceptors are activated, the more functional oxygen is transported to the mitochondria [20], especially in the places where mitochondria cluster the most, which are: brain, muscles and ganglia [8].

Baroreflex pulses can be counted in Functional Neurometry in a statistical percentage called the baroreflex index by the author, and this calculation only provides assurance that functional oxygen has reached the vasomotor centers in sufficient quantities, when it accounts for 90% or more [16].

The third category, called hemodynamics, addresses the functioning, with active and constant movement, of the mechanoreceptors, indicating that there is a good flow in the displacement of blood at the level of blood respiratory microcirculation [16], from the arch of the aorta to the carotid sinus.

In the process of investigating the functioning of oxygen transport, the fourth category, entitled physiological response, also stands out, attesting the functionality of the sympathetic and parasympathetic systems made possible through the thermoregulation sensor located in the annular proximal phalanx [20]. This category evaluated in this study has been mentioned in the literature as a strong indicator of some type of food reaction (intolerance, allergy, or hypersensitivity), when the peripheral temperature of patients is below 31.5°C.

Quantitative electroencephalogram (QEEG) of the trainers' QEEG method (TQ-7)

Trainers' QEEG Method (TQ-7) was organized by the author Peter Van Deusen [9]. The TQ-7 method uses an amplifier with four simultaneous 24-bit channels and a maximum sampling rate of 512 samples per second; each channel has a 0.2 Hz high-pass filter, and the signals are analyzed by a program called BioExplorer software [21].

Bioexplorer was developed by Cyber Evolution Inc. for real-time acquisition [22], processing, display, recording and reproduction of biological signals. It allows the user to graphically create a setup (or "design") to process the raw signals from the Q-Wiz amplifier [23] by interconnecting different processing, display and audio objects for biofeedback and neurofeedback. Processing objects include various types of low-pass, band-pass, and high-pass filters. The signals are translated by an algorithm with Fourier transform (FFTs) and mathematical and logical operations [24].

Sample calculation using the simple random method of distribution by chi-square (χ2):

$$n = \frac{\chi^2 * N * P * Q}{e^2 * (N-1) + \chi^2 * P * Q}$$

Where: n = Size to be calculated, based on the sample of patients at the ICerPE.

X^2= Chi Square (3.8416).

α=0.1= > Significance level (1-α) = 90% = 0.9 = > Confidence Level.

N = Total number of patients seen annually (400).

P = 0,5 = 50% of having success.

Q = 0,5 = 50% of having failure.

e^2 = 0,1 = 10% (sampling error).

Therefore:

$$\boldsymbol{n} = \frac{3.8416 * 400 * 0.5 * 0.5}{(0.1)^2 * (399) + 3.8416 * 0.5 * 0.5} = \frac{384.16}{3.99 + 0.9604} = \frac{384.16}{4.9504} = 77.60$$

Chi-square test from the contingency table [25]

The categorical variables of the number of occurrences, that is, the frequencies, were converted into numerical variables and then analyzed using the Chi-square test with a significance level of $p \leq 0.05$*.

	Inflammatory biomarker	
	Yes	No
ADHD group, n = 61	a	b
Control, n = 32	c	d

a = ADHD with inflammatory biomarker

b = ADHD without inflammatory biomarker

c = Control with the inflammatory biomarker

d = Control without inflammatory biomarker

[a; d] = Concordant.

[b; c] = Discordant.

Results

Association between the results of the functional neurometry exam and blood biomarkers

In table 1, the results of the control group, n = 32, were described in median (Minimum-Maximum) of each evaluated category, as: anxiety control/functional reserve: 80.44 (68 - 85) [Minimum expected value of 75%]; Baroreflex index: 92.00 (88 - 95) [Expected value > 90%]; Hemodynamics: 9 (8 - 10) [Expected value ≤ 10%]; Physiological response: 32 (31 - 32.5) [Reference value: 31.5 to 32.5] (Table 1).

Functional Neurometry							
AC		**BRI**		**HD**		**PR**	
EM	Med (Min-Max)	EM	Med (Min-Max)	EM	Med (Min-Max)	ER	Med (Min-Max)
≥ 75%	80.44 (68-85)	≥ 90%	92.00 (88-95)	≤10%	9.00 (8-10)	31.5º-32.5º	32 (31-32.50)
Total patients: 93 Control, (n = 32) ADHD, (n = 61)							

***Table 1**: FN-exam of 32 male patients without ADHD-control group (CONT, n = 32).*

The frequency of patients in the control group with biomarkers indicating subclinical inflammation is described in table 2 below.

Blood biomarkers											
TL			Eo			N			SF		
	Results	%		Results	%		Results	%		Results	%
> 6000 uL	12/32	37.50	> 7	7/12	21.87	> 55%	9/32	28.12	> 150 ng/ml	2/32	6.25
CRP			Fb			VD3			IgE		
	Results	%		Results	%		Results	%		Results	%
< 0.33 mg/dL	1/32	3.12	> 335 mg/dL	2/32	6.25	< 40	11/32	34.37	> 200 UI/ml	3/32	9.37
Total patients: 93 Control, (n = 32) ADHD, (n = 61)											

***Table 2**: Biomarkers indicating subclinical inflammation of 32 male patients without ADHD-Control (CONT, n = 32).*

Categorical variables were converted into numerical variables and analyzed using the chi-square test, expressed in a contingency table with a significance level of p ≤ 0.05.*

In table 3, the results of the ADHD group, n = 61, were described in median (Minimum-Maximum) of each evaluated category, as: Anxiety control/Functional reserve: 37.12 (9.00 - 75.18) [Minimum expected value of 75%]; Baroreflex index: 87.28 (67.33 - 93.66) [Expected value > 90%]; Hemodynamics: 17.66 (12.11 - 32.50) [Expected value ≤ 10%]; Physiological response: 26.10 (21.00 - 29.00) [Reference value: 31.5 to 32.5] (Table 3).

Functional Neurometry							
AC		**BRI**		**HD**		**PR**	
EM	Med (Min-Max)	EM	Med (Min-Max)	EM	Med (Min-Max)	ER	Med (Min-Max)
≥ 75%	37.12 (9-75.18)	≥ 90%	87.28 (67.33-93.66)	≤ 10%	17.66 (12.11-32.50)	31.5º-32.5º	26.10 (21-29)
Total patients: 93 Control, (n = 32) ADHD, (n = 61)							

***Table 3**: FN-exam of 61 male patients with ADHD-ADHD group (ADHD, n = 61).*

The frequency of patients in the dysfunctional group affected in their biomarkers is described in table 4 below.

Blood biomarkers											
TL			Eo			N			SF		
RVI	Results	%		Results	%		Results	%		Results	%
> 6000 uL	44/61	72.13	> 7	54/61	88.52	> 55%	40/61	65.57	> 150 ng/ml	9/61	14.75
CRP			Fb			VD3			IgE		
	Results	%		Results	%		Results	%		Results	%
< 0.33 mg/dL	7/61	11.47	> 335 mg/dL	6/61	9.83	<40	47/61	77.04	> 200 UI/ml	20/61	32.78
Total patients: 93 Control, (n = 32) ADHD, (n = 61)											

***Table 4**: Biomarkers indicating subclinical inflammation of 61 male patients with ADHD-ADHD group (ADHD, n = 61).*

Categorical variables were converted into numerical variables and analyzed using the chi-square test, expressed in a contingency table with a significance level of p ≤ 0.05.*

Finally, in table 5 below, a significant association was observed between the frequency of ADHD patients in their biomarkers of subclinical inflammation (N = 61).

Blood biomarkers											
TL			Eo			N			SF		
Groups	Yes/No	%	Groups	Yes/No	%	Groups	Yes/No	%	Groups	Yes/No	%
Control = 32	12/20	37.50	Control = 32	7/25	21.87	Control = 32	9/32	28.12	Control = 32	2/30	6.25
ADHD = 61	44/17	72.13	ADHD = 61	54/7	88.52	ADHD = 61	40/21	65.57	ADHD = 61	9/52	14.75
p value	0.0012		p value	0.0001		p value	0.0001		p value	0,2279	
CRP			Fb			VD3			IgE		
Groups	Yes/No	%	Groups	Yes/No	%	Groups	Yes/No	%	Groups	Yes/No	%
Control = 32	1/31	3.12	Control = 32	2/30	6.25	Control = 32	11/21	34.37	Control = 32	3/29	9.37
ADHD = 61	7/54	11.47	ADHD = 61	6/55	9.83	ADHD = 61	47/14	77.04	ADHD = 61	20/41	32.78
p value	0.1724		p value	0.5579		p value	0.0001		p value	0.012	
Total patients: 93 Control, (n = 32) ADHD, (n = 61)											

***Table 5**: Association between the results for FN-exam and biomarkers indicating subclinical inflammation.*

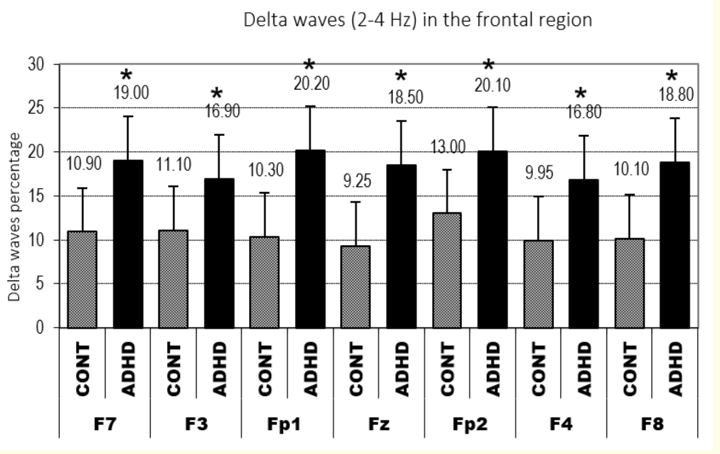
Categorical variables were converted into numerical variables and analyzed using the chi-square test, expressed in a contingency table with a significance level of p ≤ 0.05.*

Thus, the following were observed: Higher frequencies of subclinical inflammation in the ADHD group in their biomarkers, respectively: Total leukocytes [44 of 61, (72.13%), p < 0.0012]; eosinophils [54 of 61, (88.52%), p < 0.0001]; neutrophils [40 of 61, (65.57%), p < 0.0001]; 25-hydroxyvitamin D3 [47 of 61, (77.04%), p < 0.0001]; and IgE [20 of 61, (32.78%), p = 0.012], when compared to the control group in their biomarkers: Total leukocytes [12 of 32, (72.13%); eosinophils [7 of 32, (21.87%); neutrophils [9 of 32, (28.12%), 25-hydroxy-vitamin D3 [11 of 32, (34.37%); and IgE [3 of 32, (9.37%)].

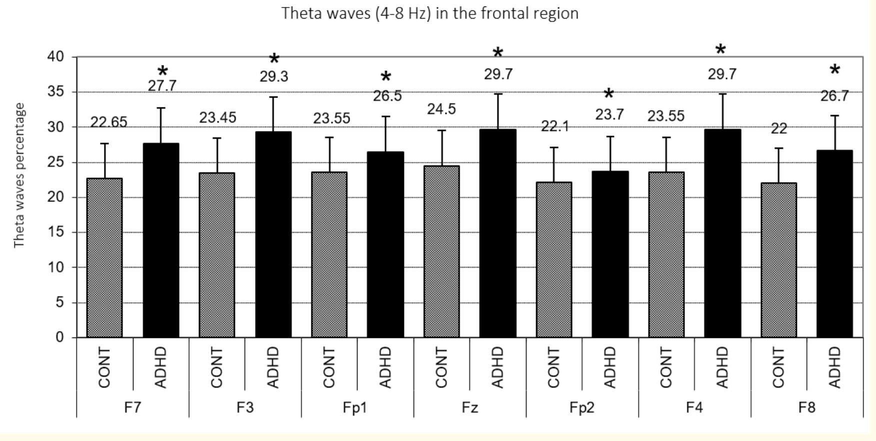
Quantitative EEG results

In graph 1, excess delta wave (1 - 4 Hz) was observed in the frontal region at the following points of the international 10 - 20 electroencephalography system: F7 = 19 (14.8 - 21.90), F3 = 16.90 (14.10 - 19.80), Fp1 = 20.20 (16.90 - 22.70), Fz = 18.50 (14.50 - 19.90), Fp2 = 20.10 (16.70 - 22.60), F4 = 16.80 (15.40 - 18.90) and F8 = 18.80 (14.20 - 20.50) in the ADHD group (p ≤ 0.05) when compared to the control (CONT): F7 = 10.90 (8.90 - 12.40), F3 = 11.10 (10.70 - 12.40), Fp1 = 10.30 (8.20 - 12.40), Fz = 9.25 (8.30 - 10.20), Fp2 = 13 (12.90 - 13.10), F4 = 9.95 (9.20 - 10.70) and F8 = 10.10 (8.90 - 11, 30) (Graph 1).

In graph 2, excess theta wave (4 - 8 Hz) was observed in the frontal region at the following points of the international 10 - 20 electroencephalography system: F7 = 27.7 (27 - 29.5), F3 = 29.3 (28.5 - 29.85), Fp1 = 26.5 (25.95 - 29.85), Fz = 29.7 (29.3 - 30.3), Fp2 = 23.7 (23.1 - 29.95), F4 = 29.7 (27.9 - 30.3) and F8 = 26.7 (23.75 - 29.3) in the ADHD group (p ≤ 0.05) when compared to the control (CONT): F7 = 22.8 (21.1 - 24.8), F3 = 23.45 (21.1 - 27.2), Fp1 = 23.55 (18 - 26.8), Fz = 24.5 (19.00 - 28.4), Fp2 = 22.1 (19.2 - 26.3), F4 = 23.55 (22.00 - 27.6) and F8 = 22.00 (19.95 - 24.3) (Graph 2).



Graph 1: *Measure, in percentage, of the amplitudes of delta waves (2-4 Hz) of the ADHD group (N = 61), compared to the measure of the amplitudes of delta waves (1-4 Hz) of the control group, CONT (N = 32). Data analyzed by the Mann-Whitney rank sum test in the sigma-stat program in version 2.0 of Jandel corporation and represented in median (Minimum-Maximum), p < 0.05*.*



Graph 2: *Measure, in percentage, of the amplitudes of the theta waves (4 - 8 Hz) of the ADHD group (N = 61), compared to the measure of the amplitudes of the theta waves (4 - 8 Hz) of the control group, CONT (N = 32). Data analyzed by the Mann-Whitney rank sum test in the sigma-stat program in version 2.0 of Jandel corporation and represented in median (Minimum-Maximum), p < 0.05*.*

Discussion

This study found an association between the dysfunctional patterns of the autonomic nervous system (ANS) of patients with ADHD, measured by the functional neurometry exam, such as: low anxiety control, low baroreflex index, compromised hemodynamics, indicating a slow blood flow velocity, physiological response with low peripheral temperature compatible with food reaction (intolerance, allergy or hypersensitivity), subclinical inflammation and excess of amplitude of delta (2 - 4 Hz) and theta (4 - 8 Hz) slow brain waves in ADHD patients when compared to the control group.

The low control of anxiety observed by the functional neurometry exam has been reported and related in the literature, as a consequence of a misalignment between adrenal and liver in the process of handling the hormones aldosterone, cortisol, adrenaline and dehydroepiandrosterone, mainly due to possible adrenal exhaustion or by the presence of non-alcoholic fatty liver disease [26].

The role of the liver, in this context, apparently is to provide the energy necessary for the adrenal to orchestrate the aforementioned hormones: as the liver does not oxidize glucose, it stores it in the form of glycogen [17] and this glycogen is activated by glucagon when the individual is fasting, so that the body makes use of this functional reserve [20].

Non-alcoholic fatty liver disease (hepatic steatosis) can result from inflammatory processes caused by caloric and nutritionally unbalanced diets, a sedentary lifestyle and excessive consumption of refined carbohydrates, which, in the long term, stimulate lipogenesis via the metabolic pathway [27].

Inflammation in the case of these individuals with ADHD seems to originate from allergenic and/or inflammatory foods [28], such as: wheat, bovine milk and derivatives, dyes, preservatives, flavor enhancers and sausages [18] or the presence of pollutants [19]. Thus, the focus of this study is not on inflammation caused by pathogens, such as viruses and bacteria, but on subclinical inflammation.

In this sense, in order to observe subclinical inflammation, in this study, the results of patients were used within the following criteria of reference values: total leukocytes (above 6000) [29], C-reactive protein (above 0.33 mg/dL) [30, 31], fibrinogen (above 333 mg/dL) [32,33], low 25-hydroxyvitamin-D3 (below 40 ng/mL) [34] and IgE (above 200 IU/ml) [35,36].

To consider the criterion of subclinical inflammation, from the total leukocytes above 6000, this study considered several findings [13-15,21,37] who showed consensus regarding values, on average, above 6000 mm^3 of total leukocytes as a strong indicator of subclinical inflammation.

C-reactive protein (above 0.33 mg/dL) was used as a parameter due to the classic study by Ridker., *et al*. (2000) [31] carried out with 28,263 female patients in a 3-year follow-up, which showed that CRP values above 0.33 mg/dL confirm the presence of a chronic inflammation with high risk of cardiovascular events.

The same eligibility criteria, outside the reference of the normal statistical curve of the laboratories, were used to choose the fibrinogen reference value (above 333 mg/dL). Thus, the study by Wildman., *et al*. (2005) [33] guided the maximum parameter of fibrinogen, indicating the advance of chronic inflammation.

Also in this context, the criterion for choosing vitamin 25-hydroxy-vitamin-D3 (below 40 ng/mL) followed an epidemiological study carried out by Melamed., *et al*. (2008) [38], where data from NHANES III were used, collected from 1988 to 1994 and carried out with 13,331 adult individuals of both genders with a mean follow-up of 8.8 years. The result was 1,806 deaths, with 43% from cardiovascular diseases, 26% from cancer deaths, 6% from infectious diseases and 5% from external causes and that people with serum vitamin 25-OH-vitamin-D3 levels between 40 - 49 ng/mL had a lower mortality rate.

The total IgE biomarker can be indicated to investigate the occurrence of allergic reactions [35], in addition to being suitable for suspected diseases caused by parasites [39]. When it comes to allergic reactions, the increase in IgE is due to the consumption of allergenic foods, such as bovine milk [27] and gluten [40] and this increase in IgE activates mast cells that release histamines, causing rhinitis, atopic dermatitis and asthma [41].

Subclinical inflammation can make it difficult for blood to move to vasomotor centers, decreasing the amount of functional oxygen to mitochondria at the brain level [20]. Thus, it is possible that this small deficit impairs the Krebs cycle, oxidative phosphorylation and neuron firing [42]. This biochemical imbalance can affect more the production of fast waves in the anterior cingulate cortex, mainly because they need more energy to produce high frequencies. In this sense, the increase in the amplitudes of the slow waves produced in the brainstem seems to be justified by this deficiency in the production of fast waves.

There are several findings that demonstrate a higher percentage of slow waves, compared to the percentage of fast waves, mainly in the frontal region of patients with ADHD. Most studies highlight the theta/beta ratio [6,37,43].

This study, although not analyzing the theta/beta ratio, corroborated the finding that there is an increase in the amplitude of Theta waves in patients with ADHD when compared to controls. But the great revelation of this study seems to have been the observation of a significant increase in delta wave amplitudes in patients with ADHD, when compared to the control group.

An interesting finding by Kaga., *et al*. (2020) demonstrated a significant reduction in oxygen transported by hemoglobins in patients with ADHD [44]. Although there is a methodological difference between this study and that of Kaga., *et al*. (2020), the significant reduction in oxygen found in the study by Kaga., *et al*. (2020) seems to indicate a consonance with the findings of high amplitude Delta waves (2 - 4 Hz) found in this study.

Another recent study by Frohlich [45] established that consciousness appears to decrease with increasing Delta waves (2–4 Hz), which may explain the reduced concentration in patients with ADHD.

The congruence between the aforementioned studies can be better understood through the reasoning of the main function of the Delta wave (2 - 4 Hz), which is to enable restful sleep, facilitating the work of the cerebrospinal fluid (CSF) in the removal of beta-amyloid proteins [46]. Thus, it seems possible to think that, if the highest amplitude of Delta wave is to be expected in moderate and deep sleep, but, an awake person with high amplitude of Delta waves may indicate that they have low functional oxygen at the brain level, which may have been caused by subclinical inflammation.

Conclusion

Physiological aspect

The Functional Neurometry exam indicated low anxiety control and functional oxygen in patients with ADHD due to adrenal insufficiency and/or liver overload, low baroreflex index, hemodynamics with reduced blood flow velocity and/or low temperature in the proximal annular phalanx, indicating possible food incompatibility.

Biochemical aspect

Subclinical inflammation caused by allergenic and inflammatory foods was also observed.

Electrophysiological aspect

High amplitudes of Delta and Theta waves were observed in patients with ADHD, which seems to indicate a consequence of subclinical inflammation and low functional oxygen at the mitochondrial level of the brain.

Thus, the functional neurometry test, blood biomarkers indicative of subclinical inflammation, and high results of delta and theta brain wave amplitudes, when associated with the clinic, can help in the diagnosis and treatment of ADHD.

Conflict of Interest

The authors declare no conflicts of interest.

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