The Theta/Beta Ratio as an Indicator of Evolution in Pediatric Patients Treated for Attention-Deficit/Hyperactivity Disorder (ADHD)

A Retrospective Study

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Abstract: This study was performed to assess whether the theta/beta ratio can be regarded as an indicator of pediatric patients' evolution while receiving treatment for ADHD. This required a spectral analysis of the electrophysiological power output from several channels with reference at the vertex (Cz). The files and EEG signals of sixteen clinical cases, which included children and adolescents from 4 to 16 years of age, were analyzed. The analysis of the EEG signals was performed using the Fast Fourier Transform (FFT) to obtain the frequency bands. Patients were under pharmacological treatment for at least one year and had at least 2 EEG studies. The results indicate that a good correlation exists between the theta/beta ratio and the patient's clinical evolution. 42% of the patients who had 3 or more EEG's, showed good correlation ($r > 0.9$), which was coherent with their good clinical evolution. 33% showed linear tendency ($0.63 < r < 0.73$), with variable response and recovery tendency. 25% had bad correlation ($r < 0.3$), also with variable treatment response. These results relate to poor adherence to the pharmacological treatment.

1 INTRODUCTION

The attention-deficit/hyperactivity disorder (ADHD) is recognized as the main behavioral disorder of children and adolescents, with 2.4 to 19.8% worldwide prevalence (Polanczyk et al., 2007). This neurobehavioral disorder is characterized by a difficulty in focusing and maintaining attention for a long time, plus impulsivity and hyperactivity (Ruiz and Sauceda, 2012).

The clinical diagnosis of ADHD is complicated due to many factors, like the difficulty in assessing objectively the degree of attention, hyperactivity and impulsivity, based on subjective information provided by informants. The presence of other neurological diseases and other clinical problems related to attention deficit are other main difficulties.

The National Initiative for Children's Healthcare Quality (NICHQ) Vanderbilt rating scale is useful for detection of ADHD in children and adolescents, and includes the assessment of comorbilities, such as oppositional defiant disorder, anxiety and depression(Wolraich et al., 2012)(Wolraich et al., 2003)(Becker et al., 2012).

Monastra et. al (Monastra, 2008), found that a substantial body of scientific support exists that associates ADHD with two primary neurophysiological changes: most patients showed excessive power in theta frequencies and suppressed beta power over frontal and central midline regions. A minority of them exhibited hyperarousal or no evidence of cortical slowing over these regions. Meta-analysis of the sensitivity and specificity of the theta/beta power ratio to differentiate patients with ADHD from healthy peers has indicated an accuracy level comparable with or exceeding that of commonly used behavioral rating scales.

The usefulness of the theta/beta ratio, which is increased in comparisons to controls with no neurological disorder, has been proved by several authors (Monastra, 2008) (Steven Snyder et al., 2008). The increased theta relative power and

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theta/beta ratio and decreased beta relative power are consistent with a meta-analytic review (Steven Snyder and Hall, 2006). In a prospective study (Quintana et al., 2007), rating scales readily classified inattentive, impulsive, and/or hyperactive symptoms as being due to ADHD, whereas only EEG was specific. The use of theta and beta power has produced more sensitivity and specificity in the detection of ADHD in a diverse clinical sample, rating scales and EEG were both sensitive markers. EEG sensitivity of 94% and specificity of 100%, was obtained whereas for ADHD-IV ratings scale sensitivity of 80% and specificity of 22% was obtained. Based on these statements, the quantitative analysis of EEG (QEEG) is recommended to support the diagnosis of ADHD, in wich the theta/beta ratio is relevant.

Pharmacological treatment of ADHD is recommended in children and adolescents with this characteristic behavior to prevent problems and develop a proper conduct at home, school and with peers. There are a variety of drugs that help to improve the patient's school performance, personal interactions, life quality and self-esteem. The treatment must be individualized and is important to consider the possible occurrence of adverse drug reactions to changes in therapy (Graham et al., 2011). Better results have been shown when patients receive both pharmacological and psychosocial therapy (Fogelman and Kahan, 2007). Non adherence to treatment is common in these patients, so the clinical evolution may vary depending on compliance or adherence to prescribed treatment.

Monitoring the therapeutic drug is important to follow the progress of ADHD symptoms, showing when the patient responds favorably to treatment and detecting cases in which the pharmacotherapy is not being effective, allowing to search causes or change the treatment schedule. For this, ratings scales and performance tests can be used (Vaquerizo-Madrid, 2008)(Herrán Paz et al., 2014), however, the same subjectivity is recognized, the questionnaires NICHQ Vanderbilt for parents and teachers, is useful for this purpose (Wolraich et al., 2012)(Becker et al., 2012), but based on the findings of Snyders et al. (Steven Snyder and Hall, 2006), (Steven Snyder et al., 2008), the EEG analysis could be useful for therapeutic monitoring of the patient clinical evolution.

Considering that ADHD has a characteristic pattern useful for its diagnosis, this retrospective study was performed in order to assess whether the theta/beta ratio can be regarded as an indicator of the evolution of pediatric patients receiving treatment for this neurobehavioral disorder.

2 METHODS

2.1 Patients Files

This is a retrospective, non-randomized study. Clinical files of sixteen ADHD pediatric and adolescent patients were screened. There were 12 male and 4 female with mean age of 9.33 ± 3.4 years (range 4 - 16 years). The weight mean was 49 ± 23.78 kg (21.61 - 95.34 Kg) and the height mean was 1.43 ± 0.74 m (1.17 – 1.75 m). A specialist on neurological disorders made ADHD diagnosis based on DSM-IV clinical assessment, structured interview and EEG. The NICHQ Vanderbilt ratings scale was found in five cases and these results were also considered to evaluate the presence and severity of the symptoms of ADHD. Patients with ADHD diagnosis, comorbilities (like oppositional defiant disorder or conduct disorder, anxiety and depression) and that were under pharmacological treatment were included. The analysis of EEG signals of children and adolescents with ADHD diagnosis, who received pharmacological treatment for at least one year and have at least 2 EEG studies (67 studies considered in total), is presented. Exclusion criteria included a history of seizure, schizophrenia, bipolar disorder, dissocial disorder and known serious medical problems, metal plate or metal device in the head.

EEG studies were performed according to International 10-20 System with at least 1 year apart. The analysis of the EEG signals was performed using Fast Fourier Transform (FFT) to obtain frequency bands: delta (0.5–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–12.5 Hz), beta (13.0– 31 Hz) and sub-divisions: delta 1 (0.5–1.5 Hz), delta 2 (2 – 3.5), and beta 1 (13.0– 20.5 Hz) y beta 2 (21 – 31.5), the periodogram and the power ratio of theta/beta bands.

Patient outcome was assessed based on medical records, remission reports from NICHQ Vanderbilt ratings scale and analysis of EEG signals (2 to 6 EEG's per patient).

2.2 EEG

EEG studies were obtained using a digital device for brain electrical activity mapping, Cadwell 32 ch. EEG Amplifier, EASY II v. 2.1. The person responsible for placing the electrodes and obtain

records of EEG's has training and experience in such procedures. Electrodes were placed in accordance with the International 10-20 System, using a 19 electrode cap, with a ground electrode at Fz and linked ears (A1 ad A2) reference. The impedance is ≤ 10 KΩ

EEG's were obtained with subjects lying down and sleeping after a sleepless night. Specifications for digitizing signals include a sampling frequency of 200 Hz a notch filter at 60 Hz and a pass band 3 dB from 0.5 to 31.5 Hz 50 Hz Interference suppression: ≥3 dB. The channels selected for data analysis, are located in fronto-temporal sites, these regions are related with the ADHD behavioral problems.

2.3 Data Processing

Data processing was made on certain steps:

1. Segment elimination based on presence of artifacts, this procedure was made visually.
2. Data filtering, a pass windows of 0.5-31.5Hz and a notch filter at 60Hz were used.
3. The following frontal and temporal channels were used: FP1, FP2, F3, F4, F7, F8, T3, T4, T5, T6 and Fz. Power spectrum (based on Fast Fourier Transform) was obtained for the whole EEG record.
4. Calculate power bands: delta (0.5-3.5Hz) theta (4-7.5Hz) alpha (8-12.5Hz) and beta (13-31.5Hz).
5. Get ratio Theta/beta.

2.4 Statistical Analyses

We hypothesized that clinic evolution of pediatric ADHD patients under pharmacologic treatment would follow changes in the theta/beta ratio through time.

Theta/beta ratio has been recognized as a characteristic pattern of this neurobiological disease, we think that patients under treatment will improve health, and theta/beta ratio will decrease significantly. A paired T-test was used to compare the initial and final theta/beta ratios at 95% confidence interval. A good linear correlation between theta/beta ratio versus time under treatment will show a good clinical evolution and good adherence to the treatment. A linear tendency will show a variable response with improvement tendency. A bad linear correlation will be associated with a variable response and slight improvement or without clinical improvement.

3 RESULTS

3.1 Physical Characteristics

Medical files of sixteen child and adolescent ADHD patients were studied retrospectively. They where 12 male and 4 female with mean age of 9.33 ± 3.4 years. Four cases had two EEG studies and twelve had three to 6 EEG's. The patients were taking stimulants like methylphenidate, and other drugs like: magnesium valproate, lamotrigine, risperidone, and others for comorbilities treatment.

3.2 EEG

Table 1, shows the theta/beta ratio for the 16 cases, for each electroencephalographic study. Theta/beta ratio decreased in most cases (87.5%, n=14), one case (6.25%) without changes and other case had an increment of the theta/beta ratio. The Theta/beta ratio decrease was related to a good clinical evolution. Initial and final EEG studies were compared for each case using a paired T-test, a significative difference was found at 95% confidence interval.

Table 2 shows correlation coefficients obtained from patients with 3 or more EEG's (12) and this was related with the clinical evolution, considering retrospective analysis of clinical histories. Considering only 12 such cases, 41.66% of this patients (5) had a good clinical evolution, this is coherent with a good linear correlation between theta/beta ratio versus time under treatment, correlation coefficients (r) were 0.977 ± 0.015, range: 0.991 to 0.951.

Four cases (33.33%) shown a linear tendency, their mean correlation coefficient was r=0.666 ± 0. 045, varied from 0.731 to 0.627.

Three cases (25%) shown a very low correlation coefficients r, with mean of 0.206 ± 0.156, range varied from 0.310 to 0.026.

These coefficients were associated with a good, variable or bad clinical response, characterized by periods with variable adherence and periods of discontinuing the therapy.

For cases with only two EEG (n=4), clinical evolution was assessed according to medical records, three of them had a good evolution and one case was bad.

Table 1: Relation theta/beta and patient's clinical evolution.

case	Theta/beta ratio each year of treatment, mean (SD)									R	Clinical Evolution
1	10.58 (3.58)	4.54 (1.87)	5.71 (1.73)	5.55 (2.16)	N.D.	3.70 (1.87)				-0.731	Variable Remission
2	5.85 (2.34)	4.49 (1.44)	N.D.	3.45 (0.85)	N.D.	N.D.	2.95 (1.00)	2.02 (0.25)		-0.952	Good
3	10.03 (3.09)	6.39 (1.88)	4.18 (1.82)	2.70 (0.67)						-0.98	Good Remission
4	11.77 (4.12)	10.59 (5.05)	9.94 (4.80)							-0.985	Good Remission
5	8.59 (2.93)	N.D.	8.19 (2.75)	N.D.	N.D.	N.D.	N.D.	N.D.	5.13 (1.71)	-0.991	Good
6	2.63 (1.00)	N.D.	N.D.	2.43 (0.58)							Good
7	4.24 (1.55)	4.67 (1.32)									Bad
8	7.22 (2.31)	5.61 (1.73)	N.D.	2.30 (1.42)	4.94 (1.60)	4.88 (0.87)				-0.628	Variable PI
9	7.06 (3.83)	14.14 (5.43)	9.54 (3.56)	4.40 (1.55)	6.11 (2.41)	3.32 (1.09)				-0.651	Variable Remission
10	3.29 (0.90)	2.40 (0.61)									Good
11	4.29 (1.33)	5.98 (1.74)	3.63 (1.35)	3.43 (0.87)						0.281	Variable SPI
12	21.42 (8.31)	16.96 (6.12)	6.92 (5.04)							-0.976	Good Remission
13	8.18 (2.75)	5.12 (2.03)	7.22 (2.18)	N.D.	6.04 (1.80)	4.65 (3.07)				-0.654	Variable PI
14	9.11 (3.62)	6.61 (2.98)	10.50 (4.18)	9.11 (3.20)						0.31	Variable Bad
15	3.91 (1.71)	0.89 (0.30)									Good
16	3.59 (1.69)	N.D.	N.D.	6.81 (2.19)	4.28 (1.29)	3.38 (0.85)				-0.026	Variable PI

SD: Standard deviation**, R:** Correlation coefficient, **PI:** Patient Improvement , **SPI:** Slight patient improvement.
N.D.:No data available

Table 2: Linear correlation coefficients of the theta/beta ratio.

Linearity		%	Mean (SD)
Good (n=5)	R > -0.95	41.67	-0.997 (0.015)
With Tendency (n=4)	-0.73 > R > -0.63	33.33	-0.666 (0.045)
Low (n=3)	-0.03 > R < 0.31	25.00	-0.206 (0.156)

SD: Standard deviation

4 DISCUSSION

Patients were taking pharmacological treatment and most of them had frequent periods of nonadherence to pharmacotherapy, with periods of improvement and relapse associated with such phenomenon.

Five patients had NICHQ Vanderbilt questionnaire, these rating scales were assessed by a psychologist. The information obtained from these rating scales answered by parents and/or teachers was included in Table 1, and was considered for assessment of patient's clinical evolution. In all these cases (n=5), results were: "in remission" or "without ADHD symptoms".

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Theta/beta ratio decreased in most cases (87.5%, n=14), one case (6.25%) without changes and other case had an increment of theta/beta ratio.

50% of patients (n=8), had good clinical evolution, 43.75% had a variable response and 12.5% had bad clinical response. Poor adherence to treatment was associated with variablity in theta/beta ratios and in their response to pharmacological therapy. Pharmacological treatment with this sample was varied and interrupted in several occasions and resumed after patients worsening.

The main problem related with pharmacotherapy in these patients was low adherence at the treatment. 100% of cases discontinued treatment for weeks or even months at least once. When this happened, a new EEG was obtained and the patient reinitiated treatment. Then the EEG's changes are not related directly with the time of treatment. Studies of pharmacy claims databases and treatment studies have shown that the prevalence of medication discontinuation or nonadherence is between 13.2% to 64% and medication nonadherence is common in childhood/adolescent ADHD (Adler and Nierenberg, 2010).

Previous studies had found that a minor percentage of children diagnosed with ADHD, may show excessive beta activity in their resting state EEG, generally associated with a negative response to methylphenidates and dexamphetamines (Clarke, et al., 2001), however this pattern was not present in these study cases. In other study(Steven Snyder et al., 2008), the theta/beta ratio was obtained in order to identify ADHD patients in three age groups: 6-11, 12-15 y 16-18 years. The EEG was obtained in resting state with close eyes. In comparison with our results in patients under the same age group. The theta/beta ratio in this studio was 7.4 ± 3.3 and 4.1 ± 1.1 for the first and second group of age, while in our study, the theta/beta ratio obtained before treatment was: 7.12 ± 3.1 for the patients who were in the group of age of 6-11 years (n=12), the theta/beta ratio obtained on patients after treatment was 5.11 ± 2.83 (n=9) and 3.14 ± 1.16 (n=5) for the first and second group of age respectively.

Figure 1 show the patients' clinical evolution, classified as: Good, variable with patient improvement, variable with slight patient improvement and bad, corresponding to sixteen cases studied. In order to relate this observations with the theta/beta correlations obtained in twelve of sixteen cases, we grouped the last two categories in only one (variable with slight patient improvement and bad).

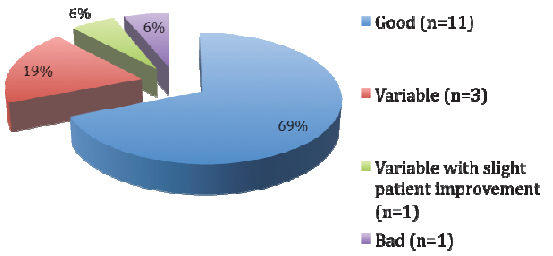

Fig. 1: Patients' clinical evolution, according medical valoration.

There is some future work pending for other studies, an example could be a study in which EEG signals from a given sample are taken under different states as resting state with closed eyes and sleeping state and compare results. Another example of future work could be the automate of the process of EEG data analysis in a system such that the theta/beta ratio could be given to the doctor in minutes and this information could be used to help ADHD diagnosis.

4.5 Limitations

First, a small sample was examined in this study, a study with a larger sample size will be required.
Second, a single psychiatric clinical site for the current study which limits the generalizability of the results.

Third, we focused in theta/beta ratio but other patterns may be useful to evaluate patient evolution.

5 CONCLUSIONS

Theta/beta ratio obtained from EEG signal analysis can be an indicator of clinical evolution of ADHD patients. The main factor for variability in response to changes in theta/beta ratio is a reflect of nonadherence to pharmacotherapy, with associated periods of improvement and relapse.

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