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The use of quantitative electroencephalography as a marker of severity of patients with autism spectrum disorder

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***Abstract*---**Autism spectrum disorder is a neurodevelopmental disorder with increasing prevalence over the past years. Its grading depends on a time-consuming Scales like CARS, ADOS and GARS scales. Our aim is to study if quantitative EEG can be used as a marker of ASD severity. This is a cross sectional study conducted in the period from September 2021 till March 2022. It included 53 patients (41 males and12 females, with age ranging between 3 and 12 years) diagnosed by an experienced psychiatrist according to DSM5 criteria. Patients were recruited from 4 autism centers in Al-Hillah city. All patients were assessed by history, physical examination and Gilliam autism rating scale (GARS 3). Then they undergo quantitative electroencephalographic recording in awake state. The study results showed that spectral power of delta wave both total and regional were significantly increased as the severity of ASD symptoms increased, while alpha spectral power was decreased with increasing severity of ASD. Beta and theta spectral power was unchanged. Also, at cut off value of power spectrum of delta of =27 Mv, give 75% sensitivity and 100 specificity for grading severe ASD. We conclude that the spectral power of delta activity can aid in the assessment and grading of ASD.

***Keywords*---**quantitative electroencephalography, ASD, gilliam autism rating scale, power spectrum analysis.

Introduction

Autism spectrum disorder (ASD) is a diverse group of conditions characterized by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviors, such as difficulty with transition from one activity to another, a focus on details and unusual

reactions to sensations[1]. Autism is known as a “spectrum” disorder because there is wide variation in the type and severity of symptoms people experience [2].The World Health Organization (WHO) estimates the international prevalence of ASD at 0.76%; however, this only accounts for approximately 16% of the global child population [3].

The diagnosis of ASD is done depending of DSM5 criteria, which consist of core symptoms that must be present before setting the diagnosis of the disease. Other diagnostic tests commonly used is a time-consuming scale that incorporate DSM5 criteria into a calculating scheme that enable the objective diagnosis based on numerical rather than subjective analysis. However, these scales are time consuming, needs cooperation between the investigator and the data provider like parents, teachers or caregivers of the patient. This subjects the scaling system to potential errors of poor cooperation, misunderstanding of questions, inability of caregiver to memorize the answers and others. In addition, the specificity of instruments was vulnerable to risk of bias[4-5-6]

Aim

This study aims to test for the presence of EEG abnormalities and their types, asses if the QEEG is sensitive enough to be used as an assessment tool in grading ASD severity level.

Patients and Methods

This cross-sectional study was carried out in the period of September 2021 to march 2022 on 53 children diagnosed with ASD (41 males and12 females), with age ranging between 3 and 12 years. All of them fulfilled the criteria of Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) by experienced psychiatrist[7]. All the children included in this study were identified and recruited from the autism centers in AL-HILLA city in Iraq, including AL-IMAM HUSSAIN center for autism, BABYLON center for autism and speech rehabilitation, MALAK AL-RAHMA center for autism, and AUTISM rehabilitation center.

Exclusion criteria: association with another neurological or chronic medical conditions (e.g. epilepsy), any association with a known genetic disease (e.g. Down syndrome and tuberous sclerosis), or those taking medications affecting the neurological status or EEG findings during the study period. All children were subjected to thorough history taking and full clinical examination with specific emphasis on neurological examination. The severity was assessed via the Gilliam Autism Rating Scale-third edition(GARS-3)[8], EEG recording and QEEG analysis were done for all studied children.

Electroencephalogram recording

The EEG recording was obtained under an eyes-closed condition for up to 30 min. The EEG was recorded using 18-electrode EEG machine CONTEC/China, with a sampling rate of 500 Hz. The settings were set on low-pass filters of 35.0 Hz, high

pass filter of 0.5 Hz, and a 50-Hz notch filter. The children were fitted with a 18-electrodes cap according to the standard 10–20 international EEG configuration.

Quantitative Electroencephalographic Analysis

For QEEG analysis, the collected data were transformed into frequency domain using computerized algorithms (i.e. Fourier Transform and Welch Method), and a scalp map of different frequency bands is obtained. After elimination and removal of artifacts, the record was divided into 8-10 sec. epochs, which were subjected to Fourier power spectral analysis and application of the Hanning window band pass, to determine the magnitude of each frequency band in microvolt. The frequency bands were classified into delta (0.5–4 Hz), theta (>4–8 Hz), alpha (>8–12 Hz), and beta (13–35 Hz). Data from 16 electrode sites, including FP1, FP2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, and O2, were analyzed. The results were used to calculate the following QEEG measures: (i) the absolute power: the amount of energy in Uv^2, (ii) the relative power: the percentage of total power within each frequency band. (iii) the coherence.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 23.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percent. Quantitative data were described using mean and SD. Significance of the obtained results was judged at the 5% level. Statistical tests used included: Student's t-test, ROC curve analysis, correlation test, and multinomial logistic regression.

Ethical approval

This study was approved by the committee of publication ethics at Babylon university/college of medicine, and verbal consent of participation was obtained from the children`s parents or their care-giver.

Results

Gilliam autism rating scale-3rd edition GARS-3 was done for all the children with ASD. Cases with mild severity represented 15.09% (8/53), moderate severity 54.71% (29/53), whereas 30.18% (16/53) had severe form.

Quantitative electroencephalographic spectral power findings between different severity levels

The statistical analysis showed significant increase of delta wave power in all brain regions as the severity of the ASD increases, with P value <0.001. alpha wave also demonstrated an increase in power seen in the right hemisphere and in the total power with a p value <0.005. On the other hand, neither theta frequency nor beta frequency displayed significant change with increase of the ASD severity.

Delta wave power at deferent head regions	ASD severity level		
	Mild	Moderate	Severe
Frontal	15.7 ± 3.6 aa	20.4 ± 2.8 bb	29.9 ± 2 cc
temporal	11.9 ± 2.4 aa	19.6 ± 3.7bb	27.3 ± 5.3cc
Central	16.1 ± 3.1aa	21.8 ± 2.7 bb	28.9 ± 3.7 cc
Prieto-occipital	18.2 ± 3a	21.4 ± 4 bb	28.8± 6.9 cc
Left hemisphere	16.2 ± 3.1aa	22.3 ± 2.3 bb	28.6 ± 3.6 cc
Right hemisphere	16.2 ± 2.7aa	25.1 ± 1.9bb	30.4 ± 3.8 cc
Total delta power	15.5 ± 2.3aa	20.8 ± 2.3bb	28.7 ± 2.7cc

Values are expressed as mean ± standard deviation

a, aa significant difference between mild and moderate at $p<0.05$ and $p<0.01$ respectively
b, bb significant difference between moderate and severe at $p<0.05$ and $p<0.01$ respectively.
c, cc significant difference between mild and severe $p<0.05$ and $p<0.01$ respectively

Table (1): distribution of Delta wave power according to ASD severity

Alpha wave power at deferent head regions	ASD severity level		
	Mild	moderate	Severe
Frontal	4.9 ± 1.5	4.5± 2	3.9 ± 2.3
Temporal	4.5 ± 2	3.9 ± 1.8	4.8 ± 5.4
Central	6.5 ± 1.6	5.5 ± 1.7	5.8 ± 4.8
Prieto-occipital	6.1 ± 2.2	6.5 ±3	7.4 ±7.6
Left hemisphere	6.4 ± 1.7	4.6 ± 1.8	5.2 ± 4.9
Right hemisphere	6.9 ± 1.9a	4.7 ± 1.5	5.2 ± 4.5
Total delta power	6.6 ± 1.4 a	4.7 ± 1.6	5.2 ± 4.7

a, significant difference between mild and moderate at $p<0.05$
Values are expressed as mean ± standard deviation

Table (2): distribution Alpha wave power according to ASD severity

Beta wave power at deferent head regions	ASD severity level		
	Mild	moderate	Severe
Frontal	1 ± 0.5	0.9 ± 0.8	1 ± 0.5
Temporal	1 ± 0.9	0.6 ± 0.3	0.8 ± 0.5
Central	1 ± 0.5	0.9 ± 1	1.1 ± 0.7c
Prieto-occipital	1.1 ± 0.5	0.9 ± 0.9	0.9 ± 0.5
Left hemisphere	0.99 ± 0.6	0.9 ± 0.7	1 ± 0.7
Right hemisphere	1.1 ± 0.9	0.9 ± 0.6	0.9 ± 0.4
Total delta power	1 ± 0.7	0.9 ± 0.7	1 ± 0.5

Values are expressed as mean ± standard deviation
c significant difference between mild and severe $p<0.05$

Table (3): distribution of Beta wave power according to ASD severity

Theta wave power at deferent head regions	ASD severity level		
	Mild	moderate	Severe
Frontal	16.5 ± 3.8	17 ± 5.9	17.9 ± 6.7

temporal	14.6 ± 3	14.6 ± 5.8	17.7 ± 6.7
Central	16.2 ± 2	23 ± 9	25.4 ± 7.3
Prieto-occipital	16 ± 1.9	22.8 ± 8.5	25.1 ± 6.9
Left hemisphere	15.6 ± 3.2	18.8 ± 6.3	20.8 ± 7.9
Right hemisphere	16.3 ± 3.3	18.7 ± 5.9	20.9 ± 6.6
Total delta power	15.9 ± 3	18.7 ± 5.8	20.9 ± 6.9

Values are expressed as mean ± standard deviation

Table (4): distribution of Theta wave power according to ASD severity

Correlation between autism index and qEEG data

Statistically significant correlation between the autism index and the spectral power of the delta waves in regions was found with p value<.001, while alpha waves demonstrated a significant reduction in power as the autism index increased with p value>-0.1, this is seen in both left and right hemispheres, central head region, and total alpha. Other wave frequencies showed insignificant correlation with the increment in the autism index. Neither the absolute power of the total nor the regional theta and beta waves was significantly associated with the disease severity index.

qEEG Power at different head regions	r value	P value
Delta frontal	0.810	0.000
Delta temporal	0.692	0.000
Delta central	0.728	0.000
Delta Prieto-occipital	0.567	0.000
Delta left hemisphere	0.751	0.000
Delta right hemisphere	0.706	0.000
Total delta	0.798	0.000
Alpha frontal	0.004	0.079
Alpha temporal	0.129	0.035
Alpha central	-0.015	0.019
Alpha Prieto-occipital	0.129	0.035
Alpha left hemisphere	-0.006	0.039
Alpha right hemisphere	-0.039	0.005
Alpha total	-0.023	0.038
Beta frontal	0.091	0.519
Beta temporal	0.043	0.762
Beta central	0.048	0.735
Beta Prieto-occipital	0.035	0.802
Beta left hemisphere	0.134	0.337
Beta right hemisphere	0.02	0.822
Beta total	0.059	0.676
Theta frontal	0.128	0.362
Theta temporal	0.241	0.082
Theta central	0.224	0.108
Theta Prieto-occipital	0.163	0.243
Theta left hemisphere	0.169	0.227

Theta right hemisphere	0.231	0.096
Theta total	0.207	0.137

Table (5): correlation between autism index and qEEG parameter

ROC curve analysis

ROC curve analysis was done to find the cut-off value with sensitivity and specificity of the different qEEG parameters in determining the severity of ASD symptoms (severe ASD in comparison to mild ASD):

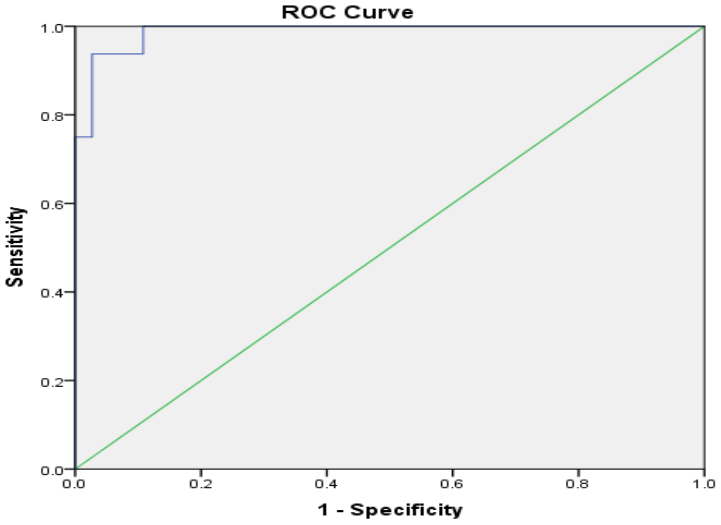

Figure (6) ROC curve analysis for assessment of ASD severity (severe ASD) by measuring the power of the total delta wave (μv)

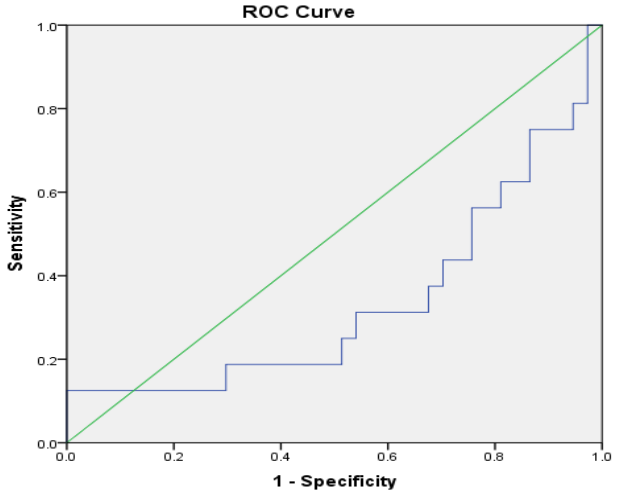

Figure (7) ROC curve analysis for assessment of ASD severity (severe ASD) by measuring the power of the total alpha wave (μv).

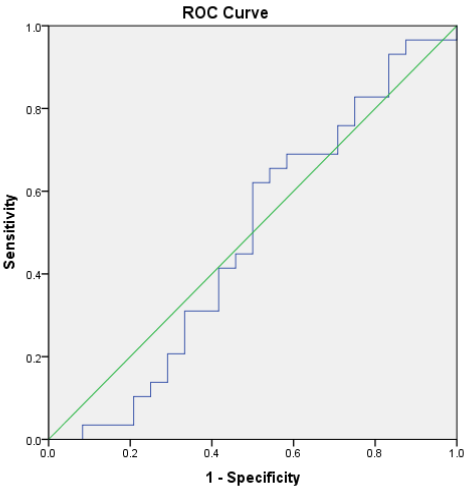

Figure (8) ROC curve analysis for assessment of ASD severity (moderate ASD) by measuring the power of the total alpha wave (μv)

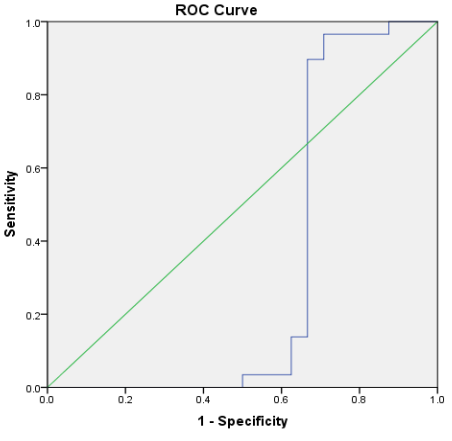

Figure (9) ROC curve analysis for assessment of ASD severity (moderate ASD) by measuring the power of the total delta wave (μv)

qEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Total delta	0.988	27.4	0.750	0.000	0.968	1.00

Table (10): ROC curve analysis of total delta in severe ASD

qEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval

					Upper bound	Lower bound
Total alpha	0.334	5.3	0.188	0.432	0.162	0.507

Table (11): ROC curve analysis of total alpha frequency in severe ASD

qEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Total delta	0.333	21.0	0.448	0.667	0.152	0.515

Table (12): ROC curve analysis of total delta frequency in moderate ASD

qEEG parameter	AUC	CUV	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Upper bound	Lower bound
Total alpha	0.484	4.6	0.448	0.458	0.321	0.647

Table (13): ROC curve analysis of total alpha frequency in moderate ASD

Discussion

In this study we found statistically significant increase of delta wave power in all cortex regions(generalized) as the severity of the ASD increased, table (1). One of the earliest studies by Cantor in 1986[9] reported increased delta-band activity in children with ASD compared to mental age-matched control subjects. as well as several other studies were able to replicate this increased delta in ASD [10-11-13]. Many studies showed an enhanced regional rather than generalized delta, increase delta in frontal head region was thought to reflects frontal lobe dysfunction, researchers stated that the increased prefrontal delta was not specific for autism; it was observed in children with mental retardation and learning disabilities without autism, as well as in children with sociocultural disadvantages[12-14-15].Delta rhythm increase in children beyond infancy was correlated mainly with learning difficulties and attention deficits[16]. This conclusion is also consistent with neuroimaging data that found widespread brain irregularities in ASD including greater total intracranial volume [17], abnormal gray matter [18], [19], white matter alteration [20], [21], and anatomical function abnormalities [22], [23]. In this study we found a positive association between the spectral power of the delta waves in all brain regions and the increment of autism index (which reflects the increase in ASD symptoms severity measured by GARS-3), On the other hand, alpha waves demonstrated insignificant reduction in power

as the autism index increased in both left and right hemispheres, central head region, and total alpha as shown in table (5).

ROC curve analysis of qEEG parameters

All previous studies measured the ROC curve to assess qEEG validity in differentiating ASD patients from controls, so up to the researcher`s knowledge, this is the first study that measure ROC curve to test the validity of qEEG in the assessment of ASD severity. The optimal cut-off value of the total delta frequency power for the diagnosis of severe ASD was (27.4 μv) with significantly good accuracy (AUC 0.988), figure (6), sensitivity 75% and specificity 100% table (10). On the other hand, the optimal cut-off value of the total alpha frequency power for the diagnosis of severe ASD was (5.9 μv) with poor accuracy (AUC 0.33) as seen in figure (7), sensitivity 81% and specificity 72%. Similarly, table (11). ROC curve analysis of qEEG parameters in the diagnosis of moderate cases results had low AUC (>50%) for all frequencies, suggesting that qEEG has poor accuracy for classifying moderate cases of ASD from mild ones. Based on ROC curve analysis of this study, delta wave results had high AUC (>90%) suggesting that this qEEG parameter has a good accuracy for classifying severe cases of ASD from mild ones, and giving the fact that qEEG is safe, non-invasive and available, it can be used as a follow up tool to monitor response to behavioral treatment, and may it can be employed for early diagnosis of high-risk infants for whom the available scales might be inapplicable.

Conclusion

Children with ASD have QEEG dysfunctions that underlie their symptomatology. QEEG testing, which is an easy, painless, and inexpensive procedure, can be a beneficial tool aiding in the assessment of children with ASD, thus paving the way for the development of tailored intervention strategies. Delta and alpha waves power spectral analysis can be used as a grading tool of ASD severity level.

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