Quantitative Electroencephalography in Children With Autism Spectrum Disorders

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Abstract- The goal of this study is to compare the brain connectivity patterns of autistic patients with those of children who are developing normally and analyzing quantitative electroencephalography in children with autism. The study included 50 children who were developing normally and 60 preschoolers who met the DSM-V criteria for autism spectrum disorder. Routine and quantitative electroencephalography were carried out on each subject, as well as a Childhood Autism Rating Scale. The electroencephalograms of 76.67% of autistic children were normal; 6.67% showed focal changes, and 16.67% showed generalized changes. While the alpha power in the central and temporal areas is significantly lower in autistic children, it is unchanged in the frontal and parieto-occipital regions. Children with autism have significantly higher absolute delta and theta band activity both globally and locally. It was shown that the total and regional absolute delta and theta power activity had a significant positive correlation with the disease severity score. Quantitative electroencephalography is a more effective tool for assessing and diagnosing children with autism spectrum disorder because it shows abnormalities in all autistic children. A correlation exists between the quantitative electroencephalography data and the disease severity score.

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Introduction

Autism spectrum disorder (ASD) refers to a group of pervasive neurodevelopmental disorders that include mild to severe impairments in social skills, expressive and receptive communication, and repetitive or stereotyped behaviors and interests (1). ASD affects the men more than women, with four affected males for every affected female (2).

Despite the existence of many studies and researches and also recognized mental illness in children and teenagers, the exact pathomechanism of ASD is unknown. Numerous factors have been proposed as contributing to its etiology, including genetic, epigenetic, immunological, and environmental ones (3).

It is essential to identify ASD in children as soon as possible to greatly enhance their outcomes. It is essential to have trustworthy screening and diagnostic tools that should be quick and simple to use, inexpensive to administer, and accurate when filled out by both clinicians and parents to facilitate early identification (4).

Electroencephalography (EEG) allows for the direct real-time observation of the electrical activity produced in the cortex, which can be recorded and analyzed (5). A resting EEG "standard-EEG" recording will be frequently inspected visually by an EEG specialist, or they will interpret the outcomes of an automated mathematical analysis that converts the raw waveform data into distinct frequency ranges known as "quantitative EEG" or QEEG measures (6,7).

QEEG is becoming more popular, and studies of neurodevelopmental disorders, particularly ASD, are using it more frequently. It aids in assessing the variety of behavioral disorders, treatment outcomes, and responses,

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among other things (8). The area that is frequently the underlying cause of the symptoms that are currently being observed can be found by analyzing the brain wave patterns in the QEEG (9).

In this study, the QEEG of a group of children with ASD will be compared to that of youngsters who are developing normally, and any changes (if any) will be correlated with sex and the Childhood Autism Rating Scale (CARS).

Materials and Methods

Prospective case-control research was carried out at the Autism Center at the Child Welfare Teaching Hospital in Baghdad Medical City from December 12, 2019, to June 1, 2021. The study was approved by the Institutional Review Board (IRB) of Al-Nahrain University's College of Medicine (Decision No. 286. Date: 23/10/2019). The child's parent provided their written consent.

Participants

The study included 60 preschoolers who met the DSM-V autism criteria (11 females and 49 males). The control group consists of 50 typically developing children with similar sex and age distribution who do not meet the diagnostic criteria for any pervasive developmental disability.

Children with autism who also had another neurological or medical condition, epilepsy, a motor, visual, or auditory impairment, inborn metabolic errors, or who were taking medication throughout the study period were excluded.

Methods

History and clinical examination

A complete medical and physical history as well as patient demographics were gathered. We clinically assess ASD using DSM-IV criteria, which also include mental and neurological examinations.

Childhood autism rating scale (CARS)

In addition to a 15th domain that rates general impressions of autistic people, CARS consists of 14 domains that evaluate behaviors related to autism (10). The ratings are based on the "peculiarity, frequency, and duration" of the rated activity and range from 1 to 4, with 4 being the most abnormal. A total score ranging from 15 to 60 is produced. Mild to moderate autism is indicated by scores between 30 and 36.5, whereas severe autism is indicated by scores between 37 and 60 (11).

Sleep EEG and QEEG

The EEG and QEEG measurements were analyzed during Stage II sleep. The signals were recorded by an EEG device (Nihon Kohden, Japan) using electrode positioning that adhered to 10-20 international standards (12). The EEG was monitored after using 50 mg/kg of chloral hydrate to fall children to sleep (13).

Nineteen scalp electrodes were positioned using a bipolar montage at the following locations: Fp1, Fp2, F7, F3, F4, F8, Fz, T3, C3, C4, Cz, T4, T5, Pz, P3, P4, T6, O1, O2. We kept the electrode impedances at 5 Kohm. A 30-minute recording was used. Sleep EEG data were classified as "Yes" or "No" for the following two criteria: normal or epileptiform discharges that can be localized or widespread.

The digitized EEG is processed by QEEG utilizing a variety of algorithms and displays based on spectrum analysis. It examines the signal distribution across several frequency bands after dividing the continuous frequency range into defined bands. Theta (4-7.5Hz), alpha (8-12Hz), and delta (0.5-3.5Hz) frequency bands were identified (14,15). QEEG was used to analyze the absolute power, which was measured as the average power V in each frequency band or wavelength and the total frequency spectrum (16).

Before the quantitative analysis preprocessing stage, all artifacts were eliminated, and the recorded data was filtered to improve the signal-to-noise ratio. The signal is divided into equal-length (10-second) epochs, which are then visually inspected to weed out any obvious artifacts. Following that, 0.1 Hz low, 15 Hz high, and 50 Hz notch-frequency filters are used to remove any remaining artifacts.

By converting the acquired data into the frequency domain using computer algorithms and the "Fast Fourier Transformation," a scalp map of different frequency bands was produced. The total and regional absolute power (frontal, temporal, central, and parieto-occipital regions) was calculated using the outcomes.

Statistical analysis

All statistical analyses were performed using IBM Corporation's SPSS statistical software, version 26. On quantitative variables, a normality test (Shapiro-Wilk test) was carried out.

The Student t-test or analysis of variance (ANOVA) was used to compare variables with a normal distribution. Variables with more than two groups were compared using the analysis of variance (ANOVA). The Mann-Whitney U test was used to analyze non-normally distributed variables and the median and range were

reported for each variable.

Chi-square was used to examine categorical variables, which were presented as counts and percentages. Alpha, delta, and theta band diagnostic significance was evaluated in the context of autistic children and control discrimination using the receiver operating characteristic (ROC) curve. $P<0.05$ was chosen as the statistically significant level.

Results

Demographic data of children with ASD

Half of the autistic children (50%) have a positive birth history (asphyxia or jaundice), while the other half (50%) have a negative birth history. According to the autistic severity score, there are 7 cases of severe ASD (11.67%), 22 cases of moderate ASD (36.67%), and 31 cases of mild ASD (%51.67).

A family history of ASD proved to be positive in 12 (20%) of the cases, while it was observed to be unrelated in 48 (80%) of the cases. There were three levels of education for the parents: tertiary, secondary, and primary. Twenty-four mothers (40%) have completed a tertiary degree, compared to 34 fathers (56.7%), 14 mothers (23.3%) have achieved a secondary degree, and 22 mothers (36.7%) have completed a primary degree. Regarding place of residence, 53 patients (11.7%) live in urban areas, compared to 7 children (83.3%) who reside in rural areas. Fathers and mothers had average parental ages of 31.92 years and 37.47 years, respectively as indicated in Table 1.

The EEG records for 46 (76.67%) of the autistic children were normal, while the records for 4 (6.67%) had abnormal focal alterations and the records for 10 (16.67%) had abnormal generalized abnormalities. Table 2 shows no evidence of a relation between the EEG pattern of the autism group and the severity of autism ($P=0.542$).

Table 1. Demographic data of children with ASD

Demographic data		Children with ASD No. 60	
		Number	%
Birth history	Negative	30	50
	Positive	30	50
ASD severity score	Mild	31	51.67
	Moderate	22	36.67
	Severe	7	11.67
Family history of ASD	Positive	12	20
	Negative	48	80
Mother education stage	Tertiary	24	40
	Secondary	14	23.3
	Primary	22	36.7
Father education stage	Tertiary	34	56.7
	Secondary	9	15
	Primary	17	28.3
Residency	Rural	7	11.7
	Urban	53	83.3
Parents' age (years) Mean±SD	Mother	31.92±5.23	
	Father	37.47±6.41	

ASD=autism spectrum disorder; Primary education=primary school or elementary school; Secondary education=secondary school or high school; Tertiary=post-secondary (higher)

Table 2. EEG pattern with the severity of autism

Severity of Autism	EEG pattern (N)			χ^2	*P*
	Generalized	Focal	Total		
Mild	3	2	5		
Moderate	5	2	7	3.09	0.542
Severe	2	0	2		

QEEG power spectrum analysis

Table 3 shows that children with ASD had significantly higher absolute total delta and theta power as well as regional (frontal, central, temporal, and parieto-occipital) power as compared to children with normal development ($P<0.001$). Absolute total alpha power for patients was noticeably higher than for controls ($P<0.001$). In comparison to controls, patients' absolute

power in the central and temporal alpha bands decreased significantly on a regional level (*P*=0.012 and *P*=0.002, respectively). The regional frontal and parieto-occipital absolute powers, on the other hand, were the same in both groups.

QEEG data and gender

The total or regional absolute delta/theta and alpha power of QEEG waves did not significantly differ between boys and girls with ASD (Table 4).

Table 3. QEEG wave parameters in patients and controls

EEG wave Absolut power (μV^2)	ASD n=60	Controls n=50	*P*
Total delta	17.52±3.9	12.29±2.58	<0.001
Frontal	14.54±4.65	7.05±2.34	<0.001
Central	15.85±5.26	9.96±2.78	<0.001
Temporal	13.58±4.45	10.43±3.42	<0.001
Parieto-occipital	16.53±4.38	11.59±3.38	<0.001
Total theta	11.63±2.18	9.0±1.96	<0.001
Frontal	9.7±2.32	5.22±1.58	<0.001
Central	10.98±2.53	7.69±2.15	<0.001
Temporal	9.4±2.49	7.56±2.69	<0.001
Parieto-occipital	11.1±2.46	8.58±2.59	<0.001
Total alpha	5.72±1.2	4.72±0.77	<0.001
Frontal	4.34±1.34	4.36±1.77	0.957
Central	5.37±1.45	6.24±2.03	0.012
Temporal	4.55±1.55	5.73±2.32	0.002
Parieto-occipital	5.93±1.83	6.32±1.69	0.251

ASD=autism spectrum disorder

Table 4. Association of absolute power of QEEG with gender in patients with ASD

EEG wave Absolut power (μV^2)	Males n=49	Females n=11	*P*
Total delta	17.24±3.55	18.75±5.2	0.247
Frontal	14.33±4.42	15.46±5.74	0.469
Central	15.38±4.4	17.94±8.0	0.147
Temporal	13.22±4.39	15.17±4.54	0.191
Parieto-occipital	16.15±4.0	18.14±5.68	0.176
Total theta	11.41±2.19	12.61±1.91	0.100
Frontal	9.56±2.23	10.3±2.71	0.348
Central	10.8±2.34	11.82±3.27	0.225
Temporal	9.18±2.19	10.36±3.52	0.156
Parieto-occipital	11.0±2.45	11.45±2.55	0.595
Total alpha	5.67±1.23	5.96±0.9	0.463
Frontal	4.31±1.45	4.48±1.3	0.721
Central	5.4±1.41	5.23±1.7	0.733
Temporal	4.5±1.56	4.8±1.58	0.574
Parieto-occipital	5.9±1.8	6.1±2.0	0.793

The disease severity score and QEEG data

In children with ASD, the absolute total delta band, as well as regional frontal and temporal delta power (*P*<0.001), central (*P*=0.003), and parieto-occipital (*P*=0.001), all showed a significant correlation with the disease severity score. Additionally, there was a significant correlation between the disease severity score and absolute total theta power (*P*=0.006), regional frontal, central, and temporal (*P*<0.001), and parieto-occipital (*P*=0.021). However, there was no significant correlation between the regional alpha wave and the absolute total alpha power with disease severity score (Table 5).

Diagnostic value of QEEG absolute power

Using the receiver operating characteristic (ROC) curve, absolute alpha, theta, and delta power were assessed for their diagnostic utility in the context of patient-control discrimination. The result is shown in Figure 1.

The area under the curve (AUC) of delta activity was 0.872, 95% CI=0.809-0.935, *P*<0001. At the cutoff value

of delta=14.15, the test's sensitivity and specificity were 80% and 70%, respectively.

Theta's band AUC was 0.809, 95% CI=0.729-0.888, *P*<0001. At the cutoff value of theta=9.8, the test's sensitivity and specificity were 80% and 66%, respectively.

The alpha band AUC was 0.8750, 95% CI=0.66-0.839, *P*<0001. The test's sensitivity and specificity were 70% and 66%, respectively, at the cutoff value of alpha=5.05.

Table 5. Association of absolute power of QEEG with CARS

EEG wave Absolut power (μV^2)	Mild (N=31)	Moderate (N=22)	Severe (N=7)	*P*
Total alpha	5.71±1.35	5.87±1.0	5.31±1.12	0.565
Frontal	4.0±1.25[a]	4.53±1.48[ab]	5.2±1.65b	0.098
Central	5.08±1.53	5.76±1.39	5.58±1.1	0.250
Temporal	4.31±1.51	4.73±1.71	5.04±1.16	0.425
Parieto-occipital	5.9±2.0	6.13±1.77	5.47±1.05	0.709
Total delta	15.36±2.7[a]	19.4±3.49[b]	21.41±4.25[b]	<0.001
Frontal	12.09±3.84a	17.26±3.57b	16.8±5.55b	<0.001
Central	13.66±3.93a	18.17±5.63b	18.23±5.71b	0.003
Temporal	11.29±3.67a	15.9±4.16b	16.46±3.15b	<0.001
Parieto-occipital	14.64±3.68a	17.91±4.1b	20.41±4.38b	0.001
Total theta	10.78±1.88[a]	12.48±2.24[b]	11.63±2.18[b]	0.006
Frontal	8.45±2.0a	10.72±1.76b	12.06±1.82b	<0.001
Central	9.57±2.0[a]	12.4±2.33[b]	12.77±1.28[b]	<0.001
Temporal	8.22±1.96a	10.25±2.1b	11.88±2.89b	<0.001
Parieto-occipital	10.26±2.42a	12.0±2.21b	11.91±2.33ab	0.021

CARS=Childhood Autism Rating Scale; Different small letters indicate significant differences

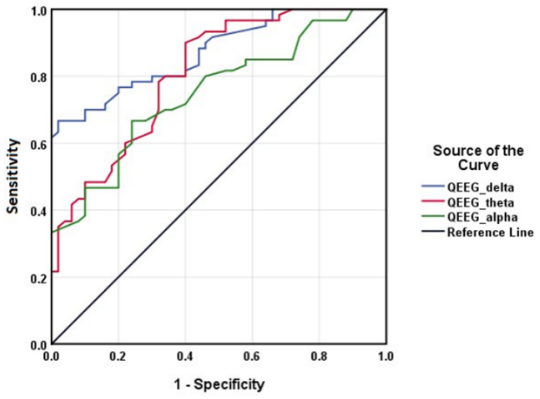

Figure 1. ROC curve for the absolute power of different QEEG waves in the context of discrimination of ASD cases from controls

Discussion

In the current study, 76.67% of children had normal EEG records while only one-fourth (23.34%) of non-epileptic children with ASD had epileptiform discharges on their EEG records that showed focal spikes or generalized discharges. Such abnormal activity was identified during sleep and a brief EEG recording. Children with autism have shown epileptiform discharges during sleep studies, which are typically thought of as co-morbid conditions with the same underlying pathophysiology as epilepsy (17,18).

According to several research studies, the prevalence of epilepsy in individuals with autism ranges from 5% to 68% (19-22), which is higher than the prevalence of epilepsy in general population (0.6-1%) (23,24). The heterogeneity of the groups tested, age range of the sample, sex, severity of the symptoms, duration of the EEG recording, and inclusion or exclusion of any co-occurring medical disorders all likely contributed to this wide variation.

Additionally, there are variations in the prevalence rate due to differences in how ASD diagnosis is carried out. However a lower rate of intellectual disability and a lower risk of epilepsy, may be seen in more recent studies using DSM-5 criteria (25,26). Only severe autism and its associations with intellectual disability and epilepsy were studied in the past.

These correlations between ASD and epileptic EEG results support the theory that a brain disorder may predispose an individual to develop another neurological disorder. Similarly, there are more ASD diagnoses in children who have seizures (27,28).

Previous research found that EEG epileptic alterations were frequently indicative of more severe forms of autism and were more frequently linked to lower intellectual functioning and more severe dysfunctional behaviors (25,26,29). However, there was no association between the EEG results and the severity of the illness in this study. This discrepancy may be partially explained by the small sample size of participants (7 out of 60) with severe illness scores. Due to their hyperactivity, denial of any sensory touch, and poor intellectual abilities, those with more severe cases present a challenge in this study and make the sleep EEG recording necessary. The conclusions of this study are based on a single short-term EEG study, which has the potential to be biased and yield false-negative findings. This is an important finding because it emphasizes the significant issue of false negatives, particularly with EEG tests (6), and the fact that a negative test result does not always imply the absence of pathology.

Because abnormal EEG is considered a biomarker of cortical dysfunction (21), they provide evidence that autism is a neurobiological disorder (30). These epileptic episodes are believed to interfere with standard cerebral processing, further impairing patients with ASD cognitive function (21,31).

The total absolute and local delta-theta activity in this study was significantly higher in patients than in controls. This might point to improper frontal-posterior neuronal integration as well as hyper- or hypofunction in the targeted region, particularly the frontal lobe. On the entire scalp, there were more pronounced absolute delta and theta frequency bands, which is consistent with the results of other studies (14,32,33).

This conclusion has been supported by previous research showing that autism is associated with abnormal brain connectivity patterns, frontal lobe enlargement, and damage to the neuronal integrity of the frontal lobe (34,35). Theta activity is excessive in children with mental illnesses like attention-deficit/hyperactivity disorder and learning disabilities (36). The prevalence of delta rhythm in children after infancy has been linked to learning disabilities and attention deficits (37).

Participants with ASD displayed elevated left frontal and prefrontal theta activity, according to research by Larrain-Valenzuela *et al*., (38) and Kawasaki *et al*., (39). They claimed that prefrontal involvement is consistent with reduced ability to switch between mental sets and highly regulated operation. In baseline conditions, theta rhythm spectral power was lower in children with early autism than in healthy children (40). Excessive theta activity was frequently seen in children with executive functioning and mental activity problems, such as attention deficit hyperactivity disorder and learning disabilities (33).

Overall, in this study, the alpha-band activity was also prominent; it decreased in the temporal and central regions but did not influence the frontal or parieto-occipital regions. The ASD children's deficit in behavioral imitation and inability to imitate a given task may be the result of abnormal mirror neuron activity (41).

Similarly, the alpha band was strengthened in the central region (42), and it was dominated in the mid-frontal and temporal regions (32,43). The absolute power of the alpha band was higher over the frontal, parietal, midline, and occipital regions (32,42). In contrast, it was lower over the temporal and frontal/prefrontal regions (44). Contrary to the studies mentioned above, other research has not found any evidence that the alpha wave patterns are altered in ASD (45,46). The results of the study may be significantly influenced by the age of the subjects and whether subjects with intellectual disabilities were included. Study sample demographics are very different from the other.

The findings of this study revealed a relationship between the absolute delta and theta bands with the severity of illness as determined by CARS. Many researchers did not conduct correlational analyses to determine the connection between abnormal EEG patterns and the severity of various clinical features of ASD. Gamma activity was positively correlated with cognitive delay in ASD (47), abnormal left frontal asymmetry was linked to higher levels of stress and anxiety (42), and increased prefrontal delta power was linked to cognitive delay in ASD (32). Finally, a recent study found a significant correlation between QEEG results and the severity of symptoms as determined by the Calibrated Severity Score (48).

Even though boys are more likely than girls to have autism, the findings of this study showed no relationship between the sex and the absolute power of slow delta, theta, and high alpha activity, showing that changes over time in these power bands were similar in both sexes. Males and females were therefore identical during the first few years of life.

In contrast to the current study, Huberty *et al*., (49) found that girls had lower absolute power scores in the high-alpha, beta, and gamma bands. Their analysis

included 1229 EEG recording sessions from 397 unique participants (208 boys) between the ages of 3 and 36 months, recordings with a 128-channel Hydrocele net, and resting EEG recorded while infants watched videos on a monitor while sitting on their caregiver's lap in a dark room. This discrepancy is most likely because of these factors.

All children with ASD who underwent QEEG testing had abnormalities, which made it a more fruitful method of assessment. Cortical slowness and inattention, impulsivity, and hyperactivity may be associated with high delta and theta activity. The unusual regional alpha-band activity observed in this study might be the result of abnormal mirror neuron activity, which would help to explain the imitative behavior of ASD children. A significant correlation was found between QEEG results and illness severity scores.

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