Auditory Brainstem Response in Children with Autism Spectrum Disorder: A Case-Control Study

Original Article

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a group of disorders characterized by abnormal social behavior, poor communication, repetitive behaviors and atypical response to sensory information, poor auditory brainstem function in ASD could be correlated to language impairment in (ASD).

Aim: The present study aimed to investigate the abnormalities in auditory brain stem response to speech stimuli among ASD children.

Patients and Methods: This case-control study was carried out from January 2019 to December 2019. The study included 21 children with autism and 30 children in a normal control group, the mean age of patients and control was comparable, respectively (4.16 ± 1.09, 4.85 ± 1.42) with males predominate in both groups. We used DSM-V-TR criteria, Stanford-Binet intelligence scale V and childhood autism rating scale (CARS) for assessments. All children were assessed in the audiology unit as follows, basic audiological evaluation, tympanometry, Click evoked Auditory Brainstem Response to confirm the presence of wave V and Speech Evoked Auditory Brainstem Response (S-ABR). Data were analyzed by IBM SPSS version 20.0, using Chi-Square, Fisher's Exact Test, and the Mann-Whitney U Test.

Results: ABR latency of wave V (6.36 ± 0.29) and wave A (7.41 ± 0.29) were detected in the patients' group, in comparison to the control group, with a significant delay (*p<0.001*). ABR latency of wave D in patients with mild to moderate autism was delayed in comparison to patients with severe autism with a significant difference (*p= 0.03*) ABR latency of wave V, A, C, and O, in patients with severe autism, was delayed in comparison to patients with mild to moderate autism with no significant difference respectively, (*p=0.85, p=0.624, P=0.94, p=0.652*). ABR latency of wave E and F, in patients with mild to moderate autism, was delayed in comparison to patients with severe autism with no significant difference respectively (*p=0.143, p=0.066*).

Conclusion: (S-ABR) is very promising in the evaluation of children with (ASD) as regards the deficit in cognitive processing, attention, auditory discrimination.

Key Words: ABR, ASD, Auditory discrimination.

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INTRODUCTION

Autism spectrum disorder (ASD) is a group of disorders characterized by abnormal social behavior, poor communication, repetitive behaviors, an atypical response to sensory information. Autism is recognized as a "spectrum" disorder because there is a broad range of symptoms that vary in type and severity. (ASD) is diagnosed by The Diagnostic and Statistical Manual of Mental disorders (DSM-5), which is a guide formed by the American Psychiatric Association used to diagnose mental disorders[1].

Depending on the diagnostic criteria used in each study, the incidence of ASD range is between 4.5 and 59/10.000, with occurrence in males three to four-fold higher than in females, most current studies have found it to be increasing to 110/10.000[2]. ASD patients frequently suffer from Language impairment that negatively influences the social interactions previous studies found that poor auditory brainstem function in ASD was correlated to language impairment[3]. On the other hand, the underlying neurobiological mechanism of language deficits in children with ASD remains unclear. The auditory brain stem response (ABR) is a non-invasive method, which reflects the activity of the subcortical auditory pathway from the distal portion of the auditory nerve to higher midbrain structures. Several studies of the ABR response in children with ASD were carried, the most common finding was prolonged absolute latencies of waves III &V and prolonged interpeak intervals (wave I-III) & (wave I-V) which reflects damage to the brainstem in these patients,

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but these studies used one type of stimulus which is clicks (click-ABR). The brainstem response to acoustic stimuli, such as the ABR, is unstable and abnormal in ASD[4&5].

The speech-evoked auditory brainstem response (speech-ABR) is a biomarker reflect how brainstem responses to complex stimulus, it is the response to speech stimuli. In general, speech stimulus is much more complex both spectrally and temporally than clicks or tones stimuli[6]. For this reason, speech-ABR is a valuable tool in the evaluation of complex speech information processing at the subcortical level[3&7].

Speech ABR is the brainstem response to speech stimuli like (e.g., music /da/,/ba/, and /ga/), most commonly used speech stimulus is the syllable \da\, it consists of two parts the "source class" include D, E, F waves and the "filter class includes V, A, C and O waves.[7] Children with ASD exhibited deficits in both neural synchrony (timing) and phase locking (frequency encoding) during the processing of speech sounds. These deficits were negatively linked to their speech performance, suggesting that brainstem dysfunction in speech processing in children with ASD may contribute to their language impairment[6]. The amplitudes and latencies of waves in the speech-ABR were increased, after auditory training, they were shortened. This reflects that brainstem auditory processing is plastic and may be improved in ASD children after training[8].

Recently, a Large number of studies have utilized the speech-ABR as a valuable tool and non-invasive electrophysiological test to investigate auditory brain stem response to a complex stimulus like speech in developmental disorders, speech ABR evaluates auditory processing of speech stimuli subcortically[9&10]. The present study aimed to investigate the abnormalities in auditory brain stem response to speech stimuli among ASD children.

PATIENTS AND METHODS:

Patients and study design:

Fifty-one children were included in this case-control study and divided into two groups of 21 children who suffer from ASD as a case group and 30 child controls. The ASD cases & controls were matched as regard age, ranged from 3 to7 years and sex. ASD cases were diagnosed by child psychiatrists in the pediatric Department, Sohag University Hospital, this study was carried in the period from January 2019 to December 2019. Patients with the following criteria were excluded from the study, patients with a history of hearing loss, ear disease, trauma, and ototoxic drug intake or ear operations Cases had the following inclusion criteria, normal middle ear function was evidenced by normal tympanic membrane examination done by otological examination at ENT department and normal middle ear pressure, acoustic reflex thresholds examined by tympanometry at Audiology unit, Sohag University Hospital. Hearing threshold did not exceed 15 dBHL from 250Hz to 8KHz, the patients did not receive speech therapy.

The control group included 30 children, with no history of hearing loss or delayed language development. Normal middle ear functions as evidence by otological examination, tympanometry, and acoustic reflex threshold. The hearing threshold did not exceed 25 dBHL from 250Hz to 8KHz. Written consent from all parents of patients and control was taken to approve sharing in the study after a full description of the steps and the work had been carried out in the accordance with the code of the Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Ethical Committee of, the faculty of medicine, Sohag University.

Methods:

1- Evaluation of all children were carried in the phoniatric unit in Sohag, native Arabic speakers and then they divided into two groups study group child with ASD and control group normally developed children then the subsequent tests were carried

a) Intelligence quotient (IQ) was evaluated by use of Stanford-Binet Intelligence Scales V[11]

b) Diagnosis of ASD was performed by the Diagnostic and statistical manual of mental disorders, Fifth Edition (DSM. V)[12], and assessment of autism severity was performed by using the Childhood Autism Rating Scale (CARS)[13]

2- All children were assessed in the audiology unit as follow:

a) Equipment: Sound treated room IAC model 1602, Pure tone audiometry: Madsen Orbiter 922, Immittancemetry: Grason- Stadler Inc.(GSI 39), Evoked potentials system SMART intelligent hearing system.

b) Procedure: All children were subjected to

- Informed written consent from the parents

- full history taking

- Otological examination

- Basic audiological evaluation, play audiometry Air and bone conduction

- Immittancemetry including tympanometry and acoustic reflex threshold

- Click evoked Auditory Brainstem Response: to confirm the presence of wave V.

- Stimulus parameters: type: click stimulus, intensity: 90dBnHL, polarity: alternating, Presentation rate, of 13.1 p/sec, mode of delivery: stimuli were presented monaurally to the right ear via an ER3A- insert the phone.

Recording parameters: electrode montage: The active electrode was placed on the high frontal (Fz), the ground electrode on the low frontal (FPz), the negative electrode on the right side, and the reference electrode on the left side.The number of sweeps: 1024, filter: bandpasses of 100 to 1500 Hz, analysis period: 0 to 12 msec.

-Speech Evoked Auditory Brainstem Response (S-ABR):

Stimulus parameters: Type: 40-ms /da/ syllable, consists of onset noise burst during the first 10 ms and formant transition between the consonant and a steady-state vowel. The stimulus was generated by Intelligent Hearing System Company and included in speech auditory brain response software. Intensity: 80 dB SPL, polarity: alternating, presentation rate: of 11p/sec, mode of delivery: stimuli were presented monaurally to the right ear via an ER3A- insert the phone.

Recording parameters: Electrode montage: The active electrode was placed on the high frontal (Fz), the ground electrode on the low frontal (FPz), the negative electrode on the right side, and the reference electrode on the left side. There are no ear differences in speech ABR so the recordings were obtained from the right ear only[14]. All electrodes were connected to the pre-amplifier of the Smart EP equipment. Many sweeps: 4000, filter: bandpasses of 100 to 1500 Hz, analysis period: 75 msec including 15 msec pre-stimulus recording.

Response analysis: The response was identified by the presence of seven waves (V, A, C, D, E, F, O), wave V analogous to the wave V elicited by click stimuli, followed immediately by a negative trough (wave A). Following the onset response, a series of peaks (C to F) represent FFR. Offset response is represented by wave O. The wave's absolute latency, amplitude, VA amplitude, duration, area, and also V-A slope all were measured.

RESULTS:

Fifty-one children were included in this case-control study and divided into two groups of 21 patients (case group) and 30 controls with comparable age and sex with no significant difference, respectively (*p=0.091, p=0.917*). As regard family history of Autism spectrum disorder among cases and controls, respectively (28.6%, 0.0%) with a significant difference (*p=0.003*). The Incidence of consanguinity among cases and controls was respectively (38.1%, 10%) with a significant difference (*p=0.035*). Normal vaginal delivery was the most common mode of delivery among cases (61.9%) and the most common mode of delivery among controls was a cesarean section (56.7%) with no significant difference (*p=0.192*). Most of the cases and controls had no history of NICU admission, respectively (85.7%, 90%) with no significant difference (*p= 0.68*). (Table 1).

Table 1: comparison between cases and control groups regarding socio-demographic data (No=51)

Variables	Cases(n=21)	Control(n=30)	*P-value*
Gender			
Female	8 (38.1%)	11 (36.7%)	0.917*
Male	13 (61.9%)	19 (63.3%)	
Age			
Mean± S.D.	4.16 ± 1.09	4.85 ± 1.42	0.091
Median (IQ range)	3.7 (3.4 – 5.05)	5 (3.88 – 6)	
Family History			
Negative	15 (71.4%)	30 (100%)	0.003**
Positive	6 (28.6%)	0 (0.0%)	
Parent's consanguinity			
Negative	13 (61.9%)	27 (90%)	0.035**
Positive	8 (38.1%)	3 (10%)	
Mode of Delivery			
Cesarean section	8 (38.1%)	17 (56.7%)	0.192*
Normal vaginal delivery	13 (61.9%)	13 (43.3%)	
Neonatal ICU admission			
No	18 (85.7%)	27 (90%)	0.68**
Yes	3 (14.3%	3 (10%)	

- *P-value* was calculated by the Mann-Whitney U Test
- **P-value* was calculated by Chi-square test
- ***P-value* was calculated by Fisher's Exact Test
- *P-value < 0.05* is statistically significant

The audiological evaluation showed that in comparison to the control group, ABR latency of wave V (6.36 ± 0.29), wave A (7.41 ± 0.29) were detected in the patients' group with a significant delay (*p<0.001*). ABR latency of wave E, F in patients' group were also delayed in comparison to control group respectively (30.96 ± 0.74 vs 30.57 ± 0.78) and (39.81 ± 0.8 vs 39.33 ± 0.41) with no significant difference (*p=0.05*). However, the ABR latency of waves C, D, and O in the patient's group show no significant difference in comparison to the control group respectively (*p=0.202, p=0.067*, and *p= 0.228*) (Table 2).

Table 2: comparison between cases and control groups regarding ABR waves (No=51).

	Group		*P-value*
	Cases (N=21)	Control (N=30)	
Wave V			
Mean± S.D.	6.36 ± 0.29	5.71 ± 0.06	<0.001
Median (IQ range)	6.3 (6.19 – 6.44)	5.72 (5.67– 5.74)	
Wave A			
Mean± S.D.	7.41 ± 0.29	6.71± 0.08	<0.001
Median (IQ range)	7.38 (7.23 – 7.56)	6.71 (6.7 – 6.75)	
Wave C			
Mean± S.D.	17.82 ± 0.57	17.77 ± 0.17	0.202
Median (IQ range)	18 (17.5 – 18.17)	17.81 (17.64 – 17.88)	
Wave D			
Mean± S.D.	22.57 ± 0.71	22.88 ± 0.31	0.067
Median (IQ range)	22.37 (22 – 23.06)	22.95 (22.8 – 23.1)	
Wave E			
Mean± S.D.	30.96 ± 0.74	30.57 ± 0.78	0.05
Median (IQ range)	30.88 (30.69 – 31.22)	30.63 (30.28 – 30.94)	
Wave F			
Mean± S.D.	39.81± 0.8	39.33 ± 0.41	0.05
Median (IQ range)	39.5 (39.13 – 40.5)	39.41 (39.1– 39.56)	
Wave O			
Mean± S.D.	47.98 ± 1.25	47.92 ± 0.51	0.228
Median (IQ range)	47.75 (47.5 – 47.94)	47.87 (47.57– 48.25)	

• *P-value* was calculated by Mann-Whitney U Test
• *P-value < 0.05* is statistically significant

The Mean of CARS among the patient group was (34.81 ± 3.76). Percent of patients with mild to moderate and severe autism was respectively (66.7% and 33.3%). ABR latency of wave V, A, C, and O, in patients with severe autism, was delayed in comparison to patients with mild to moderate autism with no significant difference, respectively (*p=0.85, p=0.624, p=0.94, p=0.652*). ABR latency of wave D in patients with mild to moderate autism (22.8 ± 0.67) was delayed in comparison to patients with severe autism (22.09 ± 0.58) with a significant difference (*p= 0.03*). ABR latency of wave E and F, in patients with mild to moderate autism, was delayed in comparison to patients with severe autism with no significant difference respectively (*p=0.143, p=0.066*). (Table 3, 4).

Table 3: CARS among cases group (No=21).

CARS	Summary statistics
Score	
Mean± S.D.	34.81±3.76
Median (IQ range)	34 (31–39)
Degree	
Mild to moderate	14 (66.7%)
Severe	7 (33.3%)

Table 4: the relation between the degree of autism and ABR latency

Degree of autism	Mean ± SD	Median (range)	*P-value*
	Wave V		
Mild to Moderate	6.31 ± 0.21	6.38 (6– 6.63)	0.85
Severe	6.47 ± 0.4	6.3 (6.13–7.2)	
	Wave A		
Mild to Moderate	7.36± 0.23	7.38(7–7.7)	0.62
Severe	7.5± 0.39	7.38(7.13–8.2)	
	Wave C		
Mild to Moderate	17.78± 0.65	17.94 (16.38–18.75)	0.94
Severe	17.89± 0.38	18 (17.38–18.5)	
	Wave D		
Mild to Moderate	22.8± 0.67	22.75(22–23.88)	0.03
Severe	22.09± 0.58	22 (21.38–23.13)	
	Wave E		
Mild to Moderate	31.07± 0.42	30.94(30.5–32.13)	0.143
Severe	30.75± 1.17	30.63 (29–32.63)	
	Wave F		
Mild to Moderate	40.01± 0.75	39.94(38.88–41.5)	0.066
Severe	39.41± 0.8	39.13(38.63–41.13)	
	Wave O		
Mild to Moderate	47.75± 0.33	47.87(47.13–48.38)	0.652
Severe	48.43± 2.15	47.63(47.13–53.25)	

• *P-value* was calculated by the Mann-Whitney U test
• *P-value < 0.05* is statistically significant

Statistical analysis:

Data were analyzed using IBM SPSS Statistics for Windows version 20.0. Quantitative data were expressed as mean ± standard deviation, median, and interquartile range. Qualitative data were expressed as number and percentage. The data were tested for normality using the Shapiro-Wilk test. The nonparametric Mann–Whitney test was used for data that wasn't normally distributed. Chi-square (χ^2) test and Fisher's Exact Test were used for comparison regarding qualitative variables as appropriate. A 5% level was chosen as a level of significance in all statistical tests used in the study.

DISCUSSION

Autism is a developmental disorder caused by an alteration in the central nervous system, which can cause impairments in perception, social interaction, poor communication, repetitive behaviors, an atypical response to sensory information. Studies report different findings regarding electrophysiological hearing tests in individuals with autism. Among such findings, one can cite alterations in brainstem auditory evoked potentials and long-latency auditory evoked potentials[15,16,17].

BAEPs are objective measures that do not require the individual's active response. Consequently, one of the main clinical applications of BAEPs is the assessment of populations that are difficult to assess using behavioral methods, such as individuals with neurological and psychiatric disorders, including children with ASD[18,19].

In our study, all S-ABR waves were identified in all participants (Table 2). This agrees with a study done by Johnson *et al* and they reported that all the S-ABR waves were identified in all individuals included in the study[20]. While our results disagree with Hornickel *et al*, they studied S-ABR in normal individuals like Johnson *et al*, but Hornickel *et al* reported (V and A) waves in 100% of participants and waves (D, E, F, O, C) were found in (87%, 91%, 91.6%, 83.3%, 83.3%, 66%) of participants respectively[21].

As regards the absolute latency of S-ABR, there was a Prolonged absolute latency of waves V and A among the patients' group in comparison to the control group with a significant difference (Table 2), This agrees with findings observed by Russo *et al* in which absolute latencies of waves V, A, of the BAEPs were longer in the ASD group than in the control group. The

findings of Russo' study differ from the current study in which absolute latencies of waves C and F of the BAEPs were longer among the ASD group than the control group with a significant difference[22].

Results of the present study were similar to findings that were reported by Rosenhall *et al*, in which more than half (58.4%) of individuals with Autism spectrum disorder with normal hearing showed abnormal auditory brainstem evoked potentials in form of a delay in wave V. This brain stem dysfunction, affecting the sensory afferents processing through the auditory pathways as part of a generalized neurological dysfunction process that explains the abnormal autistic behavior as regards the social, cognitive and language development[23].

Our study differs from Rosenhall *et al* in which the study group was not divided by severity levels for the disorder autism spectrum while the present study reported ABR latency of wave D in patients with mild to moderate autism was delayed in comparison to patients with severe autism with a significant difference (Table 4), this may be explained by the hyposensitivity to sounds that observed among children with autism, which suggests slower neural encoding of the onset of the speech stimulus[25], more studies are required to confirm the existence of hyposensitivity to sounds among patients with mild to moderate autism more than patients with sever autism.

Our study differs from Mariana *et al* in which the absolute latency of wave V was shorter in the ASD group than in the control group with a significant difference. However, this study agrees with our study in which the absolute latencies of waves C, D, E, F, and O showed no statistically significant differences between the groups[24]. The decrease in the latency of wave V in the ASD group may be explained by the hypersensitivity to sounds that observed among children with autism, which suggests faster neural encoding of the onset of the speech stimulus[25].

CONCLUSION

Speech Evoked Auditory Brainstem Response (S-ABR) is very promising in the evaluation of children with (ASD). BAEP alterations that suggest impairments on the auditory brainstem, structural or functional alterations that interfere with the transmission of acoustic stimuli along the auditory pathway that explains the deficit in cognitive processing, attention, auditory discrimination. For a better assessment of the central auditory pathway in autistic children, further studies are needed to better characterize the electrophysiological findings of this population.

CONFLICT OF INTEREST

There are no conflicts of interest.

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