Auditory brainstem responses in children with autistic spectrum disorder

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Background
The assessment and management of autism spectrum disorder (ASD) is complex and therefore requires continuous efforts for developing evidence-based guidelines for the screening, diagnosis, and treatment of ASD. This research aims to study auditory brainstem response (ABR) in autistic children as a potential biomarker that could detect autism early during infancy as well as to study its relation to repetitive behavior.

Patients and methods
It included 60 children diagnosed with ASD according to DSM-5 among those attending the Child and Adolescent Outpatient Clinic at Elhadara University Hospital and Mamoura Psychiatric Hospital. Those with hearing or visual impairment, epileptic syndromes, psychotic illness, or other affective disorder were excluded from the study. In all, 53 (88.3%) boys and seven (11.7%) girls participated in this study. Their mean±SD age was 6.41±1.99 years. Childhood Autism Rating Scale, 2nd ed., Repetitive Behavior Scale–Revised, and audiological studies were performed with emphasis on ABR by a consultant of audiology.

Results
Statistical analysis was done on the results and the study showed that absolute latency of waves III and V on the right ear and those of waves I and III on the left ear and interpeak latencies I–III and I–V of both the right and left ears were significantly away from norms in the ASD group and latency of wave I from the left side shows a significant positive correlation with total Repetitive Behavior Scale–Revised score. This denotes that a longer duration of wave I corresponds to severity of repetitive and restricted behaviors.

Conclusion
During initial assessment of a suspected ASD case, click ABR at an intensity of 80 dB (not the usual one at an intensity of 30 dB for screening of hearing impairment) to be requested and examination of the full parameters for assessment of auditory processing and not only for excluding a hearing problem.

Keywords:
auditory brainstem response, autism, repetitive movements

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Background

Autism spectrum disorder (ASD) is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behavior and interests (World Health Organization, 2018). Repetitive and restricted behaviors represent a common problem for various psychiatric syndromes, especially in ASD, where they constitute the second dimension of diagnostic criteria (Cuccaro *et al.*, 2003; American Psychiatric Association, 2013; Matuschek *et al.*, 2016). Repetitive and restricted behaviors include a wide range of heterogeneous behavioral manifestations (Szatmari *et al.*, 2006; Bourreau *et al.*, 2009). An accurate and standardized description of these behaviors advances the understanding of this complex and heterogeneous clinical dimension of ASD (Bodfish *et al.*, 2000; Carcani-Rathwell *et al.*, 2006).

Remarkably, in autism, the basal ganglia and the cerebellum are both impacted in their motor and nonmotor domains and are recently thought to be connected via the pons through a short synaptic pathway (Subramanian *et al.*, 2017; Traut *et al.*, 2018; Fernández *et al.*, 2019).

On a behavioral level, children with autism were faster than typically developing children in their ability to detect novel auditory stimuli. Gomot *et al.* (2011) suggested that although there were no differences in terms of initial registration of novel auditory stimuli (at the level of primary auditory cortex), these stimuli were differently processed by higher prefrontal regions. Evidence of hyperactivity to auditory stimuli by fMRI were also supported by electrophysiological findings (Ornitz *et al.*, 1977; Gomot *et al.*, 2011).

The auditory brainstem response (ABR) is an auditory-evoked potential recorded as a waveform that is characterized by five waves, with the first wave (wave I) originating at the auditory nerve and the fifth wave (wave V) originating at the upper brainstem. Recent publications show that wave V latency is prolonged in infants who were later diagnosed with ASD. Prolongation of the absolute latency of wave V in ASD had a significant negative correlation with age. Some studies below the age of 18 years showed a significantly prolonged wave V in ASD. Prolonged ABR was consistent in infants and children with ASD, suggesting it can serve as an ASD biomarker at infancy (Cohen *et al.*, 2013; Miron *et al.*, 2016).

Studies provide evidence for a neurodevelopmental brainstem abnormality that is already apparent in young children with suspected ASD. ABR findings support the assertion that an auditory processing deficit may be at the core of this disorder (Roth *et al.*, 2012).

Aim

(1) To assess ABR as a diagnostic tool in infants and as a trait marker of ASD.
(2) To assess the relation between ABR and repetitive behavior, which is one of the core features of autism.

Patients and methods

A cross-sectional survey design was used on a selected sample of 60 autistic children. A consent to participate in the study was obtained from parents of all children as well as approval of the current research from ethics committee of Alexandria University.

All cases were subjected to the following:

(1) History taking.
(2) Thorough clinical examination with emphasis on neurological examination.
(3) Childhood Autism Rating Scale, 2nd ed.: the standardized Arabic edition for an established assessment for ASD among Arabic-speaking children (Akoury-DiranI*et al.*, 2013).
(4) The Repetitive Behavior Scale–Revised (Lam and Aman, 2007).
(5) Audiological examination and testing.

Every child was scheduled an appointment at the Alexandria University Audiology Unit to be examined by an audiology specialist and subjected to the following.

Basic audiological evaluation: basic audiological evaluation was done to ensure normal peripheral hearing and intact acoustic reflexes.

(a) Otoscopy for inspection of the external auditory canal and tympanic membrane.
(b) 226 Hz tympanometry and ipsilateral acoustic reflexes thresholds at 0.5, 1, 2, and 4 kHz using the tympanometer model ‘Clarinet, Inventis, Padova – Italy.’
(c) Pure-tone audiometry (PTA) was performed in a double-walled soundproof room using an audiometer (AD229E Audiometer; Interacoustics, Assens, Denmark). Air-conduction thresholds were measured using TDH39 headphones calibrated according to ISO 389. Pure-tone thresholds were 20 dBHL or less between 0.25 and 8 kHz.

ABR:

ABR audiometry refers to an evoked potential generated by a brief click or tone pip transmitted from an acoustic transducer in the form of an insert earphone or headphone. The elicited waveform response is measured by surface electrodes typically placed at the vertex of the scalp and ear lobes. The amplitude (microvoltage) of the signal is averaged and charted against time (millisecond), much like an electroencephalography. The waveform peaks are labeled I–VII. These waveforms normally occur within a 10-ms time period after a click stimulus presented at high intensities [70–90 dB normal hearing level (nHL)] (Burkard*et al.*, 2007; Hammond and Katta-Charles, 2016).

In this study, ABR was performed using Interacoustics Eclipse EP 25 (InteracousticsAssens, Denmark) in a darkened quiet room. Two channel recordings were obtained. Inverting or negative electrodes on each mastoid (reference), the noninverting or positive electrode in the Cz or FPz position on the high forehead, and the ground connection was placed on the low forehead. The electrode sites were prepared to assure that the top layer of the skin (epidermis) is cleaned and oil is removed. This ensures low skin impedance for the measurement. For this purpose,

Table 1 Distribution of children according to other psychometric tools (*N*=60)

	n (%)	Minimum–maximum	Mean±SD	Median (IQR)
CARS2		20.0–50.0	35.28±7.64	34.0 (30.0–41.75)
Mild and moderate (<36)	36 (60.0)			
Severe (≥36)	24 (40.0)			
RBS-R total		1.0–89.0	32.62±18.80	29.0 (19.0–45.0)
Stereotyped		0.0–17.0	7.85±4.47	6.50 (4.50–11.50)
Self-injurious		0.0–16.0	2.97±3.40	2.0 (0.0–4.0)
Compulsive		0.0–19.0	4.97±4.19	4.50 (2.0–7.0)
Ritualistic		0.0–16.0	4.65±3.65	4.0 (2.0–6.50)
Sameness		0.0–36.0	7.63±6.95	7.0 (3.0–10.0)
Restricted		0.0–12.0	5.03±3.16	5.0 (2.0–8.0)

CARS2, Childhood Autism Rating Scale, 2nd ed; IQR, interquartile range; RBS-R, Repetitive Behavior Scale–Revised.

Table 2 Comparison between norms and cases according to absolute latencies of waves I, III, V, and interpeak latencies I–III, III–V, and I–V (*N*=60)

	Wave latency	Normal	Cases	*T*	*P*
		Mean±SD			
Right	I	1.40±0.14	1.50±0.25	1.943	0.057
	III	3.87±0.13	3.59±0.25	5.533*	<0.001*
	V	5.76±0.24	5.51±0.32	3.480*	<0.001*
	I–III	2.44±0.10	2.09±0.31	5.983*	<0.001*
	III–V	1.84±0.18	1.93±0.21	1.812	0.075
	I–V	4.30±0.26	4.02±0.37	3.447*	0.001*
Left	I	1.37±0.10	1.46±0.18	2.434*	0.018*
	III	3.86±0.11	3.72±0.31	2.237*	0.021*
	V	5.66±0.17	5.54±0.31	1.890	0.063
	I–III	2.48±0.11	2.25±0.29	4.129*	<0.001*
	III–V	1.78±0.20	1.83±0.21	0.960	0.341
	I–V	4.33±0.20	4.07±0.32	3.836*	<0.001*

*Significant results are starred.

Table 3 Correlations between Childhood Autism Rating Scale, 2nd ed and Repetitive Behavior Scale–Revised (*N*=60)

	CARS2
RBS-R	0.263*
	0.043*

CARS2, Childhood Autism Rating Scale, 2nd ed; RBS-R, Repetitive Behavior Scale–Revised. *Significant results are starred.

skin preparation paste was used. Disposable electroencephalography electrodes were used.

After applying the electrodes, impedance was measured. Interelectrode impedance did not exceed 3000 ohms and the differences between electrode pairs were kept at below 2000 ohms.

In children who were not cooperative in PTA or PTA was not applicable, their thresholds were obtained by ABR. Thresholds were searched for at a starting level of 70 dB; if present descend in 20 dB steps, if absent ascend in 10 dB steps.

Recordings were replicated to ensure response reliability, and only reproducible waveforms were accepted at each intensity level till reaching the threshold. The stimulus was 100 μs, rarefaction, broadband click, presented at a rate of 21.1/s, with total sweeps 1000, with a time window of 20 ms.

Stimuli were delivered through IP30 insert phones. Recordings were filtered online with a 100–3000 Hz band-pass filter. The input rejection level was set to 40 μV. Only children with normal hearing thresholds were included in the study.

Then other ABR waves are obtained at 80 dB nHL for all children with the following parameters: 80 dB nHL, 100 μs, rarefaction, broadband click, presented at a rate of 21.1/s, with total sweeps of 1000, with a time window of 20 ms.

Data obtained from ABR were focusing on absolute latencies and amplitudes of waves I, III, V on both sides; interpeak latencies (IPLs) I–III, III–V, and I–V; and interaural latencies between right and left. Results were compared with normal values obtained from the audiology clinic database, from typically developing children of the same age group.

Table 4 Correlation between auditory brainstem response parameters and other scales (*N*=60)

		RBS-R score						
	CARS2	Total	Stereotype	Self-injury	Compulsive	Ritualistic	Sameness	Restricted
R I latency								
r	–0.118	0.234	0.164	0.141	0.241	0.058	0.171	0.275*
P	0.368	0.072	0.210	0.282	0.063	0.659	0.192	0.033*
R III latency								
r	–0.170	0.240	0.151	0.141	0.228	0.065	0.205	0.275*
P	0.194	0.065	0.250	0.282	0.080	0.620	0.116	0.033*
R V latency								
r	–0.163	0.246	0.147	0.155	0.232	0.059	0.214	0.280*
P	0.212	0.058	0.262	0.238	0.075	0.655	0.10	0.03*
R I amplitude								
r	–0.123	0.022	–0.093	–0.022	–0.019	–0.072	0.151	0.096
P	0.349	0.865	0.482	0.867	0.884	0.582	0.250	0.465
R III amplitude								
r	–0.196	0.165	–0.152	–0.001	–0.009	0.016	0.486*	0.148
P	0.198	0.208	0.247	0.993	0.944	0.901	<0.001*	0.258
R V amplitude								
r	–0.158	0.234	–0.140	0.060	0.063	0.043	0.548*	0.217
P	0.228	0.071	0.288	0.647	0.631	0.746	<0.001*	0.095
R I–III latency								
r	–0.202	0.237	0.137	0.137	0.212	0.069	0.224	0.266*
P	0.121	0.069	0.296	0.295	0.105	0.602	0.086	0.040*
R III–V latency								
r	–0.151	0.254	0.145	0.176	0.235	0.049	0.226	0.281*
P	0.250	0.051	0.270	0.178	0.070	0.712	0.082	0.029*
R I–V latency								
r	–0.178	0.246	0.142	0.157	0.224	0.060	0.226	0.276*
P	0.173	0.058	0.280	0.231	0.085	0.651	0.082	0.033*
L I latency								
r	–0.145	0.254*	0.190	0.153	0.266*	0.051	0.188	0.288*
P	0.270	0.050*	0.145	0.244	0.040*	0.701	0.150	0.025*
L III latency								
r	–0.169	0.253	0.154	0.155	0.241	0.059	0.217	0.293*
P	0.197	0.051	0.240	0.238	0.064	0.654	0.096	0.023*
L V latency								
r	–0.163	0.247	0.148	0.159	0.231	0.057	0.215	0.283*
P	0.213	0.057	0.260	0.225	0.076	0.667	0.099	0.028
L I amplitude								
r	–0.010	0.031	0.034	–0.032	0.003	–0.054	0.047	0.104
P	0.938	0.817	0.798	0.805	0.982	0.683	0.723	0.431
L III amplitude								
r	–0.130	0.107	0.148	0.019	0.084	0.031	0.077	0.095
P	0.321	0.416	0.258	0.885	0.522	0.813	0.559	0.468
L V amplitude								
r	–0.171	0.189	0.089	0.124	0.169	0.057	0.162	0.214
P	0.191	0.148	0.498	0.345	0.198	0.663	0.217	0.101
L I–III latency								
r	–0.184	0.248	0.128	0.152	0.221	0.064	0.232	0.291*
P	0.160	0.056	0.329	0.247	0.09	0.624	0.075	0.024*
L III–V latency								
r	–0.147	0.243	0.137	0.179	0.216	0.065	0.221	0.266*
P	0.262	0.061	0.298	0.171	0.098	0.619	0.090	0.040*
L I–V latency								
r	–0.168	0.243	0.131	0.161	0.217	0.059	0.223	0.287*
P	0.199	0.061	0.319	0.219	0.096	0.653	0.086	0.031*
Interlatency I–III								
r	–0.020	0.068	–0.048	0.081	0.057	–0.061	0.051	0.210

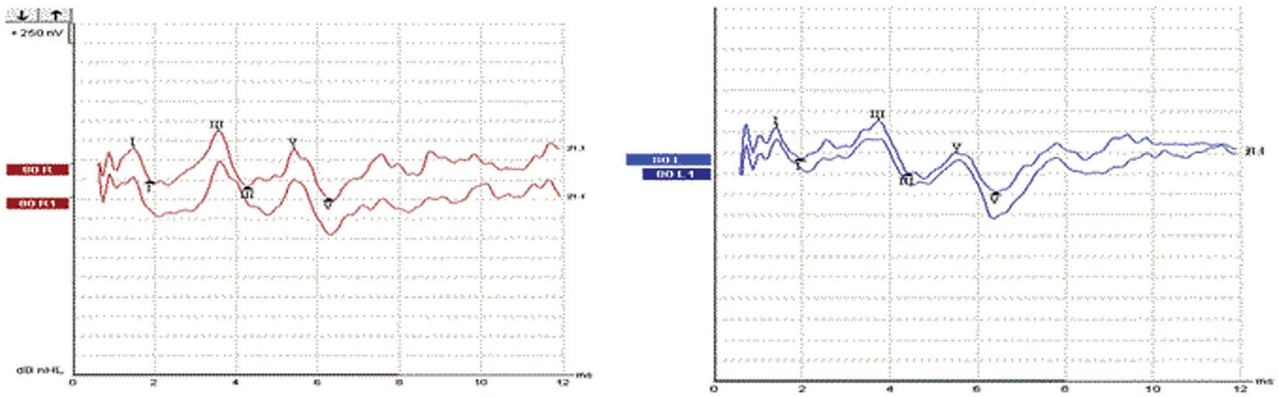
(*Continued*)

Table 4 (*Continued*)

	CARS2	RBS-R score Total	Stereotype	Self-injury	Compulsive	Ritualistic	Sameness	Restricted
P	0.882	0.607	0.714	0.538	0.665	0.642	0.701	0.107
Interlatency III–V								
r	−0.124	0.417*	0.315*	0.319*	0.441*	0.207	0.265*	0.387*
P	0.343	0.001*	0.014*	0.013*	<0.001*	0.113	0.040*	0.002*
Interlatency I–V								
r	−0.061	0.082	0.110	0.035	0.181	−0.019	−0.033	0.159
P	0.642	0.535	0.403	0.791	0.166	0.882	0.801	0.224
Interlatency V–V								
r	−0.026	0.130	0.168	0.076	0.129	−0.056	0.081	0.231
P	0.843	0.323	0.199	0.565	0.326	0.670	0.540	0.075

CARS2, Childhood Autism Rating Scale, 2nd ed; RBS-R, Repetitive Behavior Scale–Revised. *Significant results are starred.

Figure 1



ABR of one of the patients recorded at an intensity level of 80 dB nHL. ABR, auditory brainstem response; nHL, normal hearing level.

Results

Statistical analysis was done on the results and the study showed that absolute latency of waves III and V on the right ear and those of waves I and III on the left ear and interpeak latencies I–III and I–V of both the right and left ears were significantly away from norms in the ASD group and latency of wave I from the left side shows a significant positive correlation with total Repetitive Behavior Scale–Revised score. This denotes that a longer duration of wave I corresponds to severity of repetitive and restricted behaviors.

Tables 1–4 and Fig. 1.

Discussion

Regarding ABR, we measured the absolute latencies of waves I, III, and V, the interwave intervals of I–V, I–III, and III–V. Data analysis was performed at stimulus intensity levels of 80 dB SPL.

In this study, comparing the autistic group with the norms used at the Audiology Clinic in the Alexandria Main University Hospital revealed that absolute latency of waves III and V on the right ear and those of waves I and III on the left ear and IPLs I–III and I–V of both the right and left ears were significantly away from norms in the ASD group. These finding indicate that children with autism have dysfunction or immaturity of the central auditory nervous system.

On the other hand, wave I on the left side had a significant positive correlation with Repetitive Behavior Scale–Revised score. This signifies that this part of the central nervous system could be related to those specific features of ASD, yet this needs to be replicated in further studies.

Magliaro *et al.* (2010) evaluated auditory-evoked potentials in a group of autistic children, whose quantitative data analysis showed that statistically significant differences between the ASD group and the control group were found only for the ABR regarding the latencies of waves III and V and interpeaks I–III and I–V. Kwon *et al.* (2007) and

Azouz *et al.* (2014) found that the latency of wave V and waves I–V IPLs were significantly prolonged in the ASD group.

In agreement with our findings, Roth *et al.* (2012) found that all absolute latencies and IPLs were significantly prolonged in the group with ASDs compared with clinical norms, excluding IPL III–V (Miron *et al.*, 2016). This coinciding results despite the variability in ABR findings in research could be explained by the fact that the same age group has been examined (Miron *et al.*, 2018).

Taking into consideration that ABR informs us about the processing of acoustic stimuli in the brainstem, these findings may give some clinical evidence of brainstem abnormalities, which could be partly responsible for abnormal development in autistic children.

Conclusion

Absolute latency of waves III and V on the right ear and those of waves I and III on the left ear and IPLs I–III and I–V of both the right and left ears could be used in infants suspected to be autistic and it is highly correlated to repetitive behaviors.

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Conflicts of interest

There are no conflicts of interest.

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