<u>original research</u>

Exploring the Relationship Between Auditory Brainstem Response Testing and Disease Progression in Pediatric Autism Spectrum Disorder

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ABSTRACT

Objective • This study aimed to examine auditory brainstem response (ABR) test results in children diagnosed with autism spectrum disorder (ASD) to provide valuable insights for the future diagnosis and treatment of ASD. **Methods** • We conducted a retrospective analysis involving

26 children diagnosed with ASD admitted to our hospital between April 2021 and December 2022 (the observation group) and 38 children who underwent health checkups during the same period (the control group). ABR testing was administered to both groups at our hospital. We assessed differences in ABR test results between the observation and control groups and analyzed the correlation between ABR test results and the outcomes of the Autism Behavior Checklist (ABC) and Childhood Autism Rating Scale (CARS) surveys. Additionally, we examined variations in ABR test

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INTRODUCTION

Autism spectrum disorder (ASD) is a pervasive developmental disorder that primarily affects children and is characterized by abnormal communication skills, narrow interests, and stubborn behavioral patterns.^{1,2} Ongoing research into the etiology of ASD predominantly implicates genetic abnormalities, although some theories suggest potential links to perinatal brain injuries, neuroanatomy, neurobiochemistry, immune system function, and genetics.³

results among ASD children across different age groups. **Results** • In the observation group, we observed higher right ear latencies of waves I and III, as well as differences in left and right ear interpeak latencies (IPLs) of waves I-V compared to the control group (P < .05). However, the left and right ear IPLs of waves III-V were lower in the observation group (P < .05). There were no significant differences in ABR test results among ASD children of different ages (P > .05). Furthermore, we identified positive correlations between the right ear wave III latency, left ear wave I-III IPL, and right ear wave I-III IPL with ABC and CARS scores (P < .05). **Conclusions** • Children with ASD display abnormal ABR

characteristics, indicating the potential of ABR as a valuable tool for evaluating ASD progression in the future. (*Altern Ther Health Med.* [E-pub ahead of print.])

However, the pathogenesis and pathological changes underlying most clinical cases of ASD remain poorly characterized. Additionally, many children with ASD often present with concurrent conditions, such as developmental delay, intellectual disability, and attention-deficit hyperactivity disorder.⁴ Instead of a single effective medication to address the core symptoms of ASD, most children require lifelong treatment, placing a significant burden on families and society at large.⁵ Furthermore, ASD lacks specific diagnostic or unique physiological markers and physiological tests. Combined with limitations in scale-based evaluations, there is a pressing need to actively explore valuable detection techniques for the diagnosis of ASD.⁶

Auditory Brainstem Response (ABR) is a diagnostic test that assesses the function of the inner ear and neural pathways for hearing by recording brain wave activity in response to auditory stimuli, commonly used when conventional hearing screenings are challenging or when hearing issues within the brain are suspected.⁶⁻⁷ ABR test involves recording brainstem-derived evoked potentials from the scalp in response to auditory stimulation, providing a means to evaluate brainstem function.⁷ Previous studies have revealed that some children diagnosed with ASD exhibit varying degrees of brainstem dysfunction.⁸ It has been noted that some of the children with ASD exhibit increased reactions to auditory stimuli, which could be indicative of underlying brainstem disorders.⁹ Therefore, we postulate that the ABR test holds potential as a clinical diagnostic tool for ASD, offering insights into its correlation with disease progression. Our study conducted appropriate research to validate this hypothesis, aiming to contribute novel perspectives to future clinical screening and prognostic predictions for ASD.

MATERIALS AND METHODS Study Design

This study employed a retrospective design to investigate the potential utility of the ABR test in diagnosing and understanding ASD. The research involved two groups: an observation group consisting of 26 ASD cases admitted to the facility between April 2021 and December 2022 and a control group comprising 38 children undergoing concurrent physical examinations. Data from these groups were carefully analyzed to assess ABR test results, which were then correlated with clinical assessments of ASD. The study design adhered to the ethical guidelines outlined in the Declaration of Helsinki, with informed consent secured from the legal guardians of all participants.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Participants had a confirmed diagnosis of ASD based on established clinical diagnostic criteria¹⁰; (2) Participants demonstrated the ability to cooperate with medical staff for rehabilitation training and testing procedures; (3) Participants had undergone a battery of auditory tests, including 226 Hz acoustic immittance, ABR, Distortion Product Otoacoustic Emissions (DPOAEs), and Multi-frequency Steady-state Auditory Evoked Potentials; (4) Participants had no history of ototoxic drug use that could have impacted auditory function; (5) Participants did not have any other developmental abnormalities or organic diseases that could have confounded the study results.

The exclusion criteria were as follows: (1) Individuals with documented hearing loss, irrespective of its cause or severity, were excluded from the study; (2) Participants with mental retardation or other cognitive disorders that could have interfered with the study's objectives were excluded; (3) Individuals with severe somatic diseases unrelated to the study's focus were excluded to ensure the study's clarity and focus on ASD and auditory function.

Testing Procedures and Parameters

The Danish International Hearing Eclipse test system was utilized for testing children in a quiet, sound-shielded room with appropriate room temperature and minimal ambient noise <30 dB(A). Before the test, all children underwent a routine examination of the external ear, revealing no abnormalities in the external auditory canal. Subsequently, they were tested either during sleep or under

anesthesia induced by the injection of 10% chloral hydrate (0.5 mL/kg). Electrode placement included the recording, grounding, and bilateral reference electrodes positioned at the middle of the forehead, nasal root, and mastoid process, respectively.

The ABR test employed EAR tone in-ear earbuds with electrode impedance below 5 k Ω and a bandpass range of 100-3000 Hz. Short-range sound stimuli were delivered through headphones at a stimulation frequency of 20.1 per second and an intensity of 80 dB nHL. Sound polarity followed an alternating wave mode, and the sound was delivered to one ear with superimposition performed 2000 times. Each ear underwent continuous testing in 2 rounds of average superposition. Normal ranges were determined based on routine reference values from our department. Additionally, DPOAE was assessed using a MADSEN Capella otoacoustic emission instrument, recording response amplitude and signal-to-noise ratios at 0.50, 0.75, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz. A signal-to-noise ratio of \geq 6.0 dB was employed as the criterion.

Behavioral Evaluation

(1) Autism Behavior Checklist (ABC)¹¹: This assessment tool comprises 57 items, each scored on a scale of 1-4 points based on the symptom severity, with a total score of \geq 62 points indicating the presence of ASD. Higher scores correspond to more severe symptoms. (2) Childhood Autism Rating Scale (CARS)¹²: This instrument consists of 15 items assessing various aspects, including interpersonal relationships and imitation, with scores ranging from 1 to 4 for each item. A total score exceeding 30 indicates ASD, with specific ranges (31-40, 41-50, and 51-60) representing mild, moderate, and severe ASD, respectively.

Endpoints

The study examined the disparities in ABR test outcomes between the observation and control groups. Additionally, it explored the associations between ABR test results and the ABC and CARS scores among children with ASD. Lastly, the study investigated variations in ABR detection findings among ASD children of varying age groups.

Statistical Analysis

Data analysis for this study was conducted using SPSS version 23.0. Categorical variables (%) and continuous variables $(\bar{x} \pm s)$ were compared between groups utilizing the chi-square (χ^2) and *t* tests, respectively. Pearson correlation coefficients were employed for correlation analysis. *P* < .05 denoted statistical significance.

RESULTS

Comparison of Clinical Data

Initially, a comparison of the fundamental clinical data between the two cohorts of pediatric patients was conducted to ensure the reliability of the experimental results. The ages, heights, and weights of both the observation and

Table 1. Comparison of Clinical Data

Group	n	Weight (kg)	Height (cm)	Age (months)
Control Group	38	16.56±3.78	100.31±19.14	37.81±11.30
Observation Group	26	17.66±1.96	100.47±4.50	39.13±6.53
χ^2		1.531	0.096	0.593
P value		.131	.924	.555

Note: Values are presented as mean \pm standard deviation. Group comparisons were conducted using the chi-square test (χ^2) for categorical variables and the *t* test for continuous variables.

control groups were found to exhibit no statistically significant differences (P > .05, Table 1), confirming their comparability.

Comparison of Latencies for Waves I, III, and V in the Left and Right Ears

The latencies of waves I, III, and V in the left ear, as well as wave V latency in the right ear, exhibited no significant differences between the observation group and the control group (P > .05). However, the latencies of waves I and III in the right ear of the observation group, measured at (1.47±0.12) and (3.70±0.14), respectively, were significantly higher compared to the control group (P < .05, see Figure 1).

Comparison of Interpeak Latencies (IPL)

Initially, when comparing intergroup IPLs for waves I-III, no significant difference was observed (P > .05). However, for waves III-V, the observation group exhibited lower IPLs compared to the control group (P < .05). In contrast, for wave I-V, the observation group had higher IPLs than the control group (P < .05, see Figure 2).

Variations in ABR Test Results Among ASD Children of Different Age Groups

We employed the median age of children in the observation group as the threshold to categorize them. Our analysis revealed no significant differences in the latencies and IPLs of the left and right ears between children aged \leq 37 months and those aged > 37 months (P > .05, see Figure 3).

Correlation of ABR Test Results with ABC in ASD Children

Through Pearson correlation coefficient analysis, it was determined that the left ear latency exhibited no significant relationship with ABC scores in ASD children (P > .05). However, the right ear wave III latency, left ear wave I-III IPL, and right ear wave I-III IPL displayed a positive correlation with ABC scores (P < .05), refer to Table 2.

Correlation Between ABR Test Results and CARS in ASD Children

The correlation between ABR test results and CARS scores in ASD children revealed a positive association between CARS scores and right ear wave III latency, left ear wave I-III IPL, and right ear wave I-III IPL (P < .05), refer to Table 3. These findings are consistent with the above analysis.

Figure 1. Latencies of Waves I, III, and V in the Left and Right Ears



Note: Figure 1 displays waves I, III, and V latencies in both the left and right ears. (A) Left ear I-wave latency. (B) Right ear I-wave latency. (C) Left ear III-wave latency. (D) Right ear III-wave latency. (E) Left ear V-wave latency. (F) Right ear V-wave latency. Significance levels (${}^{a}P < .05$) are indicated to highlight differences.



Note: Figure 2 presents a comparison of Interpeak Latencies (IPL) in both the left and right ears. (A) Left ear I-III interpeak latencies. (B) Right ear I-III interpeak latencies. (C) Left ear III-V interpeak latencies. (D) Right ear III-V interpeak latencies. (E) Left ear I-V interpeak latencies. (F) Right ear I-V interpeak latencies. (F) Right ear I-V interpeak latencies. Significance levels (${}^{a}P < .05$) are indicated to highlight differences.

Table 2. Correlation of ABR Test Results with ABC in ASD

 Children

Ear		r	P value
Left Ear	I latency	0.426	>.05
	III latency	-0.664	>.05
	V latency	0.161	>.05
	I-III IPL	0.642	<.05
	III-V IPL	-0.342	>.05
	I-V IPL	0.016	>.05
Right Ear	I latency	-0.069	>.05
	III latency	0.594	<.05
	V latency	0.193	>.05
	I-III IPL	0.587	<.05
	III-V IPL	0.236	>.05
	I-V IPL	0.198	>.05

Note: Correlation coefficients (r) and *P* values were calculated to assess the relationship between ABR test results and the Autism Behavior Checklist (ABC) scores in children with Autism Spectrum Disorder (ASD). Correlations with P < .05 were considered statistically significant.

Figure 3. Differences in ABR Test Results in ASD Children of Different Ages



Note: Figure 3 presents the differences in Auditory Brainstem Response (ABR) test results among children with Autism Spectrum Disorder (ASD) of varying ages. (A) Left ear I-wave latency. (B) Right ear I-wave latency. (C) Left ear III-wave latency. (D) Right ear III-wave latency. (E) Left ear V-wave latency. (F) Right ear V-wave latency. (G) Left ear I-III interpeak latencies. (H) Right ear I-III interpeak latencies. (I) Left ear III-V interpeak latencies. (J) Right ear I-V interpeak latencies. (L) Right ear I-V interpeak latencies. This analysis provides insights into the age-related variations in ABR responses among ASD children.

 Table 3. Relationship Between ABR Test Results and CARS in ASD Children

Ear		r	P value
Left Ear	I latency	0.340	>.05
	III latency	-0.016	>.05
	V latency	-0.026	>.05
	I-III IPL	0.594	<.05
	III-V IPL	-0.208	>.05
	I-V IPL	0.103	>.05
Right Ear	I latency	0.224	>.05
	III latency	0.693	<.05
	V latency	-0.219	>.05
	I-III IPL	0.620	<.05
	III-V IPL	0.140	>.05
	I-V IPL	-0.165	>.05

Note: Correlation coefficients (r) and *P* values were calculated to assess the relationship between ABR test results and Childhood Autism Rating Scale (CARS) scores in children with Autism Spectrum Disorder (ASD). Correlations with P < .05 were considered statistically significant.

DISCUSSION

Children with ASD typically experience significant challenges in emotional expression and social interactions. As they age, they may face difficulties in self-care and navigating interpersonal relationships, even with their parents.¹³ The ABR test primarily records the auditory system's activity from the cochlea within the inner ear to the auditory center within the cerebral cortex. Abnormalities in Wave I suggest pathological changes in the auditory nerve fibers, inner hair cells, and spiral ganglion cells within the cochlea. Conversely, abnormalities in Waves III and V are often attributed to acoustic neuromas and intracranial brainstem lesions.¹⁴ The ABR test, being a noninvasive clinical examination tool, demonstrates sensitivity, stability, reliability, and resilience to cultural differences and age. These qualities make it a promising identification method for ASD.¹³⁻¹⁴

In this study, we observed a notable increase in wave I and III latencies in the right ear, as well as the I-V interpeak latency (IPL) in children with ASD compared to control children. Conversely, we observed a decrease in the IPLs for waves III-V in both the left and right ears. These findings imply that the ABR test results in ASD children markedly differ from those in typically developing children. Such distinctions hold considerable significance in the context of ASD differentiation.

Our finding aligns with previous research,¹⁵ providing preliminary support for our hypothesis. It suggests that these varying IPL results may be attributed to the disruption of the structural connections among auditory nerve cells, resulting in a deceleration of neuronal discharge. Additionally, the asynchrony in the synthesis and release of neurotransmitters by inner hair cells can contribute to unsynchronized nerve impulses, consequently extending latency or IPL.¹⁶

In the gamma-band brain network of children with ASD, the distribution pattern of core brain regions involved in information reception and distribution differs from that of the control group, resulting in an imbalance in information distribution.¹⁷ Therefore, the atypical expression of nerve conduction pathways in children with ASD may arise from the combined influence of multiple factors, and ABR serves as an objective evaluation tool for assessing such impairments.

ASD tends to manifest in children between the ages of 2-3 years, a critical period for brain, language, and learning development. Disruptions in the information transmission pathway of the auditory system during this period can result in subsequent challenges with information discrimination, integration, and feedback. This, in turn, can exacerbate clinical symptoms such as stereotypical behavior and narrow interests.¹⁶⁻¹⁷

The auditory sensitivity measured by ABR, particularly in response to short sounds within the 1-4Hz range, exhibits a strong correlation with the activities of auditory pathways across the cochlea, auditory nerve, and the brainstem. In the absence of peripheral hearing impairments, ABR can generally elicit precise and objective electrical responses, providing insight into the development of auditory pathways in children.^{18,19}

In this study, no significant differences were observed in ABR test results among children with ASD of varying ages. However, Miron et al.⁷ observed that younger children with ASD exhibited significantly lower wave I-III and wave I-V IPLs. They argued that there are apparent differences in the developmental maturity of the auditory system and brainstem at different ages, suggesting that auditory dysfunction in ASD may become more pronounced in older children with a longer disease duration. This discrepancy with the findings of our current study is attributed to the possibility of statistical variation arising from the limited sample size. Therefore, we intend to expand the subject pool in future to validate these observations. Moreover, considering the challenge in altering the behavioral phenotype of ASD once it has formed, and the presence of corresponding neural responses at all levels in the brainstem during children's activity, the connection between ABR latency, IPL, and behavioral phenotype can be explained by recording the associated potentials generated by the auditory nervous system in response to electrode stimulation. Based on Pearson correlation coefficient analysis, it was determined that the right ear wave III latency, left ear wave I-III IPL, and right ear wave I-III IPL exhibited a positive correlation with ABC and CARS scores in children with ASD.

Considering the shortened wave III-V and I-V IPLs observed in some children with ASD, we can tentatively conclude that ABR patterns in ASD may vary. Moreover, ABR does not necessarily rule out abnormalities in the secretion and release of other neurotransmitters or the functioning of outer hair cells responsible for hearing.^{20,21} Therefore, we propose that delicate electrophysiological changes in the auditory system can be analyzed by adjusting examination parameters such as stimulation frequency and repetition, thereby enhancing our understanding of brainstem function and the extent of hearing impairment. Clinically, tailored intervention strategies should be developed based on a child's auditory development level and age to optimize ASD treatment.

Study Limitations

While this study offers valuable insights into the potential utility of ABR testing in assessing ASD, several limitations warrant consideration. First, the relatively small sample size may limit the generalizability of our findings. Expanding the cohort size in future research could provide more robust and representative results. Second, the study did not encompass a wide age range, and further investigation across a broader age spectrum is essential to comprehensively understand the applicability of ABR testing in different developmental stages of ASD. Additionally, the study focused primarily on ABR's relationship with behavioral measures, and other contributing factors to ASD was not extensively explored. Future research should include a more comprehensive approach to explain the multifaceted nature of ASD.

CONCLUSION

The ABR test resulted in significantly irregular results in children with ASD when compared to control subjects. Notably, there was a substantial increase in wave I and III latencies in the right ear, accompanied by a decrease in wave III-V and wave I-V interpeak latencies in the right ear. Furthermore, we established a positive correlation between the right ear wave III latency, left ear wave I-III IPL, and right ear wave I-III IPL with scores on the ABC and CARS in children undergoing ABR testing. These findings suggest the potential of the ABR test as a valuable tool for assessing the progression of ASD, offering practical guidance for auditory integration training and other intervention programs for children with ASD. Nevertheless, it is crucial to acknowledge the limitation of our study, which stems from the relatively small sample size. The underlying mechanism regarding the inverse correlation between the prolongation of right ear wave III latency and the developmental level of children with ASD remains unclear and requires further comprehensive and in-depth studies.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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