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Original Article

Physiology Section

Brainstem Auditory Evoked Potential in Preterm Infants and its Relation with Gestational Age

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ABSTRACT

Introduction: Preterm births are associated with different neuro developmental abnormalities. During the last trimester of pregnancy, a part of foetal brain development occurs. Some area of the brain does not show normal growth even after the birth of preterm babies. Due to advanced obstetric and neonatal care of the present time, neonatal complications and mortality has reduced substantially. However, the preterm newborns experience many perinatal developmental abnormalities including prematurity of auditory pathway. Among the paediatric population, subjective tests for auditory evaluation are non reliable. Brainstem Evoked Response Audiometry (BERA), which assesses Brainstem Auditory Evoked Potential (BAEP), is a simple, non-invasive and an objective way of evaluating functional integrity of auditory pathway.

Aim: To assess the neurological maturation and integrity of the auditory pathway by BAEP in preterm infants with respect to the gestational age.

Materials and Methods: The present cross-sectional study was done in the Eastern region of India. A total of 74 preterm infants and 30 fullterm infants were included from the Department of Paeadiatrics, R.G. Kar Medical College, Kolkata, India. In the Department of Physiology, BAEPs were compared among preterm and full-term infants. The preterm babies were divided into three subgroups according to gestational age, Group 1 (≤28 weeks); Group 2 (29-32 weeks); Group 3 (33-36 weeks). Intergroup comparison was done by Student's t-test, ANOVA and Post-Hoc test.

Results: Preterm babies had prolonged wave I, wave V latency and I-V Interwave latency in the right ear ($p<0.05$) In Group 1, wave V and I-V latency were prolonged in both the sides. Right sided prolongation of wave I and wave V latency were present in Group 2. Left I-V interwave latency was prolonged in Group 1 than Group 3. A total of 24 preterm infants had absent waves.

Conclusion: Preterm infants had premature peripheral and central auditory pathway. Group 1 showed central pathway immaturity compared to term infants and Group 3. Group 2 showed immature peripheral pathway. Absent waves were present in all the groups but maximum in Group 3, suggestive of dysfunction of auditory pathway but exact location of pathology was uncertain.

Keywords: Intrauterine age, Neuronal maturation, Premature birth

INTRODUCTION

Preterm is defined as birth on or before the end of the last day of the 37th completed week after the starting of the mother's last menstrual period, which equates to 259 days [1]. According to recent November 2017 WHO data, every year, an estimated 15 million babies are born as preterm (>1 in 10 babies) and the number is rising [2]. Severe neuro developmental disability remains the most adverse long term outcome associated with prematurity. Hypoxic ischaemic brain injury and bilirubin brain toxicity are mostly associated with preterm and Low Birth Weight (LBW) infants [3]. Incidence of sensorineural hearing loss varies widely from 1.5 to 17% among high risk infants [4]. Early diagnosis by screening can reduce the handicap resulting from deafness. WHO estimates that every year 38,000 deaf children are born in South-East Asia. India has 6.3% prevalence rate of moderate to severe hearing impairment [5].

In preterm infants, clinical auditory evaluation is difficult. Neurological maturity of auditory system is a two phase process. The first phase is intrauterine, and is generally completed by the sixth month of gestation; at this point the peripheral auditory pathways are mature. After birth, the second phase starts and ends at about 18 months of life; at this point the auditory pathways along the central nervous system up to the brainstem reach maturity [6-8]. Another study suggests that, although the neuronal migration is completed by 20 weeks of gestational age, some part of the foetal brain development occurs during the last trimester of gestation, including myelination, glial cell migration and the development of a complex gyral pattern [9]. A part of the brain doesn't show normal growth after birth in preterm babies. In extremely preterm infants, [Extremely preterm (<28 weeks); Very preterm (28 to <32 weeks); Moderate or late preterm (32 to <37 completed weeks of gestation)] neonatal brain injury and interruption of the normal maturation of the brain result in functional impairments that appear to manifest in future life [10,11]. BAEPs are noninvasive, objective neurophysiologic assessment of auditory pathway maturation up to brainstem in paediatric population. These are obtained in response to repetitive auditory stimuli and can be recorded from the auditory pathway. BAEP study is done to evaluate the neurologic development and integrity of the auditory pathway in preterm infants by comparing the latencies of the preterm waveforms with that of the term babies.

Several authors have reported that BAEP responses in neonates and infants are affected by the maturity of the auditory system [12,13].

The BAEPs reflect the conduction along the auditory brainstem pathway. The BAEP waveform in neonates and infants is comprised of three identifiable waves (I, III, and V). In paediatric population, three components of BAEP wave is recorded and measured; Wave I- most distal portion of auditory nerve, Wave III- superior olivary complex, Wave V-inferior colliculus. Among all the waves, wave V is the most consistent wave. Wave I latency denotes peripheral auditory pathway and I-V interwave latency denotes central auditory pathway sound transmission. In premature infants, delayed wave I

means, prematurity of peripheral pathway which causes delayed auditory transmission. Immaturity of central pathway causes prolonged I-V interwave latency and it is responsible for increased central sound transmission time [14].

The BAEP waves are generated due to summated activity of large populations of neurons firing in synchrony. If the timing of neuronal activity is delayed uniformly across the cell population, delayed waves are generated [14].

According to some authors, there were abnormalities of auditory evoked potential in preterm infants [9,11]. Though, there were some contradictory views which said that, BAEP findings were similar between preterm and term infants or preterm babies along with other risk factors like hypoxia, acidosis, and prolonged intubation, had significant BAEP changes [15,16]. This creates a milieu upon which the present study can evaluate its outcome more precisely. The babies with above mentioned risk factors were excluded from the current study.

This present study evaluated, BAEP among preterm infants in comparison with normal term infants and role of gestational age on BAEP parameters. Both the groups were otherwise healthy. The study aimed to document whether preterm birth has any influence on the development of auditory pathway and if this influence is affected by gestational age. This may indicate, prematurity in CNS, for which early diagnosis and treatment are crucial for improving linguistic development and prognosis of these infants.

MATERIALS AND METHODS

An observational study was undertaken and the subjects were included by purposive sampling. BAEP data was taken from total 104 infants. Among them, 74 preterm infants were compared with 30 full term infants, taken as control group. No ototoxic drugs were given and infants were examined during natural sleep.

These preterm infants were further divided into three groups according to their gestational age and their comparison with control population and intragroup comparison were done. These groups were Group 1 (n=26) born in ≤28 weeks; Group 2 (n=30) born within 29-32 weeks; Group 3 (n=18) born within 33-36 weeks.

The calculated sample size was ≥73.76. so, on the basis of this value, 74 cases were selected.

The confidence interval was calculated as 6.75-6.99. β=0.155407. So, power of the study was 0.844593 Mean and standard deviation were derived from a previous study done in the similar settings, using the same protocol on 30 subjects. The previous study was a feasibility study. The BAEP recordings were also included in the present study.

The infants who were born as preterm and admitted in Neonatal Intensive Care Unit were advised for BERA (to evaluate BAEP abnormalities). Both inborn and outborn infants of Department of Paediatric Medicine at R.G. Kar Medical College and Hospital, Kolkata, India, were included. Along with them, infants, who were born as preterm and attended to Sick baby clinic (According to protocol of the Medical college, all the infants with history of neonatal high risk factors like premature birth, neonatal hyperbilirubinemia, etc, attended Sick Baby Clinic for a routine follow up) of Paediatrics Out Patient Department (OPD), were also included as cases.

They were advised for the same test in Applied Physiology Lab at Department of Physiology at R.G. Kar Medical College and Hospital, Kolkata, within three months of their date of birth. Control group was selected from Well Baby Clinic of paediatrics OPD, of the same hospital. The study was conducted for six months from November 2016 to April 2017, in Department of Physiology in collaboration with Department of Paediatric Medicine. The study was approved by the Institutional Ethics Committee, R.G. Kar Medical College and Hospital, Kolkata. Severely ill infants or infants with history of (H/O) neonatal jaundice, craniofacial anomalies, chromosomal disorders, intrauterine infections, birth trauma, metabolic disorders or intracranial infection were excluded. Infants with H/O recent Upper Respiratory Tract Infection or any pathology in external ear were also excluded.

The BAEPs were estimated by BERA using Neuro-MEP4, Ivanovo, Russia. Initially, parents were interviewed to fill the case record form and to gather a clinical history. External ear assessment, prior to an evaluation of hearing, was carried out and findings were documented. Parents or guardians of the infants were explained about the study and they were asked to shampoo the hair of their infants on the day before the examination and visit the laboratory on a given date. On arrival, the study protocol was explained to guardians and a proper written consent was taken. They were also instructed to wake the infants up early in the morning on the day of the test. This would ensure that the infants remain asleep during the whole recording time in order to exclude biologically derived noise. Calm and quiet but awake infants were also included for the procedure.

Their scalp and forehead were prepared with Nuprep cleaning gel for electrode placement.

The surface electrodes were used for recording BAEP. The silver cup electrodes were used and fixation was done with electrolyte paste. The electrode impedance was less than 5 kilo-ohm. The electrodes were placed at the vertex (Cz) and at both earlobes as per International 10-20 system. The earlobes, ipsilateral and contra lateral to the stimulated ear are labeled Ai and Ac respectively. The ground electrode (Fz) was placed at the forehead [14].

Mono phasic square pulse acoustic clicks of 0.1 ms were used at 11.1 pulse/second. Rarefaction clicks were used with 1 ms/div sweep speed and 0.5 microvolt sensitivity. BAEP recording was done by using 70 dB stimulus intensity in ipsilateral ear and 40 dB lower than stimulus intensity was used as masking noise in contra lateral ear [14].

Filter setting was adjusted between 100 Hz-3000 Hz. Two thousand evoked responses were averaged to get a clear waveform and two such recording were taken to assess reproducibility.

The absolute latencies of waves I, III, V and the I-V inter peak latency of BAEP were compared between the study group and control group to assess any significant difference between them. When BAEP parameters of cases were prolonged in respect to these normal range of values, or when BAEP waves were absent, both were considered as abnormal.

STATISTICAL ANALYSIS

At 70 dB intensity BAEP changes of 74 preterm infants were compared with 30 normal infants taken as control group. To compare data of main group and subgroups with control population, Student's t-test was applied and statistical analysis was done with Graph Pad Quick Calc software, California, USA. To compare data among three sub groups, one way ANOVA test was applied. Then Tukey HSD post-hoc test was done to indicate which groups were significantly different from which others. Statistical analysis was done with http://www.statpages.info software, USA. p-value <0.05 was considered as statistically significant.

RESULTS

The present cross-sectional study consisted of 74 preterm infants. Postnatal age and sex were similar with 30 full term infants, taken as control. The mean gestational age (SD) of preterm infants at birth were 30.46 (±2.87) weeks and their mean birth weight was 1.81 (±0.34) kg. BAEP parameters, latencies of wave I, wave III, wave V, and I-V interwave latency were recorded and compared between control group and total preterm population as well as subgroups of cases. The result of the entire study was represented below in the form of tables.

According to [Table/Fig-1], there were no statistically significant difference between cases and controls in respect to all four parameters in left ear whereas according to [Table/Fig-2], wave I, wave V, I-V interwave latency were statistically significantly prolonged in the right ear of the cases in respect to control population. This suggested that auditory pathway was matured on the left side, but on the right side neuronal immaturity was present in both peripheral and central auditory pathway. Among 74 preterm infants, on the left side, wave I was absent in 14; wave III, in 16 and wave V and I-V interwave latency, in 17 infants. In the right ear, wave I and wave III were absent in 19; wave V and I-V interwave latency, in 17 infants.

BAEP parameters latency (mS)	Wave present in cases	Case Mean (SD)	Control Mean (SD)	p-value
Wave I	60 out of 74	1.93 (.25)	1.9 (.14)	0.54
Wave III	58 out of 74	4.54 (.46)	4.57 (.28)	0.74
Wave V	57 out of 74	6.75 (.55)	6.63 (.2)	0.25
I-V interwave latency	57 out of 74	4.79 (.57)	4.7 (.17)	0.4

[Table/Fig-1]: Comparison of BAEP parameters in left ear between cases and controls.
mS: Milisecond

BAEP parameters latency (mS)	Wave present in cases	Case Mean (SD)	Control Mean (SD)	p-value
Wave I	55 out of 74	2.02 (.3)	1.9 (.14)	0.04*
Wave III	55 out of 74	4.6 (.4)	4.54 (.36)	0.56
Wave V	57 out of 74	6.87 (.48)	6.58 (.17)	0.002*
I-V interwave latency	57 out of 74	4.85 (.43)	4.68 (.16)	0.04*

[Table/Fig-2]: Comparison of BAEP parameters in right ear between cases and controls.
p<0.05 is considered, statistically significant (*) {In reference to reviewer comment U13-Add the value at which it is considered significant. (p<0.001 or 0.05)}

All these preterm infants were divided into three groups according to gestational age. Individual result of each group was demonstrated below.

In both the ears, wave V and I-V interwave latencies were statistically significantly prolonged among Group 1 preterm infants, in comparison with control population [Table/Fig-3,4]. This suggests neuronal immaturity in central auditory pathway of both the sides.

BAEP parameters latency (mS)	Wave present in cases	Group 1 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	22 out of 26	1.9 (.25)	1.9 (.14)	1
Wave III	21 out of 26	4.53 (.42)	4.57 (.28)	0.48
Wave V	21 out of 26	6.94 (.52)	6.63 (.2)	0.0045*
I-V interwave latency	21 out of 26	5.02 (.56)	4.7 (.17)	0.0048*

[Table/Fig-3]: Comparison of BAEP parameters in left ear between Group 1 preterm infants, n=26 and controls, n=30.
*statistically significant

BAEP parameters latency (mS)	Wave present in cases	Group 1 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	19 out of 26	1.98 (.32)	1.9 (.14)	0.22
Wave III	19 out of 26	4.47 (.37)	4.54 (.36)	0.51
Wave V	19 out of 26	6.95 (.5)	6.58 (.17)	0.0005*
I-V interwave latency	19 out of 26	4.96 (.44)	4.68 (.16)	0.0026*

[Table/Fig-4]: Comparison of BAEP parameters in right ear between Group 1 preterm infants and controls.
*statistically significant

According to [Table/Fig-5], there were no statistically significant difference between cases and controls in respect to all four parameters in the left ear whereas according to [Table/Fig-6], wave I and wave V, were statistically significantly prolonged in the right ear of the cases with respect to the control population. This suggests that Auditory pathway was matured on the left ear, but neuronal prematurity was present in peripheral auditory pathway in right ear.

BAEP parameters latency (mS)	Wave present in cases	Group 2 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	22 out of 30	1.96 (.27)	1.9 (.14)	0.3
Wave III	21 out of 30	4.57 (.51)	4.57 (.28)	1
Wave V	20 out of 30	6.74 (.66)	6.63 (.2)	0.39
I-V interwave latency	20 out of 30	4.73 (.63)	4.7 (.17)	0.8

[Table/Fig-5]: Comparison of BAEP parameters in left ear between Group 2 preterm infants and controls.

BAEP parameters latency (mS)	Wave present in cases	Group 2 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	23 out of 30	2.08 (.31)	1.9 (.14)	0.0066*
Wave III	23 out of 30	4.69 (.4)	4.54 (.36)	0.16
Wave V	23 out of 30	6.92 (.5)	6.58 (.17)	0.002*
I-V interwave latency	23 out of 30	4.84 (.49)	4.68 (.16)	0.099

[Table/Fig-6]: Comparison of BAEP parameters in right ear between Group 2 preterm infants and controls.
*statistically significant

According to [Table/Fig-7,8], there were no statistically significant difference between cases and controls in respect to all four parameters in the left and right ear. This suggests that auditory pathway was matured both in left side and right side.

BAEP parameters latency (mS)	Wave present in cases	Group 3 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	16 out of 18	1.93 (.25)	1.9 (.14)	0.6
Wave III	16 out of 18	4.53 (.48)	4.57 (.28)	0.72
Wave V	16 out of 18	6.51 (.32)	6.63 (.2)	0.12
I-V interwave latency	16 out of 18	4.56 (.38)	4.7 (.17)	0.09

[Table/Fig-7]: Comparison of BAEP parameters in left ear between Group 3 preterm infants and controls.

BAEP parameters latency (mS)	Wave present in cases	Group 3 Preterm Mean (SD)	Control Mean (SD)	p-value
Wave I	13 out of 18	1.99 (.27)	1.9 (.14)	0.16
Wave III	13 out of 18	4.62 (.42)	4.54 (.36)	0.53
Wave V	11 out of 18	6.62 (.34)	6.58 (.17)	0.62
I-V interwave latency	11 out of 18	4.7 (.24)	4.68 (.16)	0.76

[Table/Fig-8]: Comparison of BAEP parameters in right ear between Group 3 preterm infants and controls.

The p-value of only left sided I-V interwave latency indicates there was a significant difference somewhere among the different three groups [Table/Fig-9]. Tukey HSD post-hoc test is done to indicate which groups are significantly different from others.

BAEP Parameters	Groups Mean (SD)			
	Group 1	Group 2	Group 3	p-value
Lt I	1.9 (.25)	1.96 (.27)	1.93 (.25)	0.74
Rt I	1.98 (.32)	2.07 (.31)	1.99 (.27)	0.59
Lt III	4.53 (.42)	4.57 (.51)	4.53 (.48)	0.95
Rt III	4.47 (.37)	4.69 (.4)	4.62 (.42)	0.2
Lt V	6.94 (.52)	6.74 (.66)	6.62 (.25)	0.06
Rt V	6.95 (0.5)	6.92 (0.5)	6.62 (.34)	0.15
Lt I-V	5.02 (0.56)	4.73 (.63)	4.67 (.39)	0.04*
Rt I-V	4.96 (.44)	4.84 (.49)	4.7 (.24)	0.29

[Table/Fig-9]: ANOVA test for intragroup comparison of all the BAEP Parameters.
*statistically significant, Lt-left Rt-Right

I-V interwave latency of left ear was statistically significantly different between Group 1 and Group 3. This suggests, left sided central auditory pathway was immature among Group 1 in comparison with Group 3 [Table/Fig-9,10].

Group	Vs	Group	p-value
Group 1	Vs	Group 2	0.21
Group 1	Vs	Group 3	0.036*
Group 2	Vs	Group 3	0.62

[Table/Fig-10]: Post-Hoc test of intragroup left I-V interwave latency.
*statistically significant

DISCUSSION

The BAEP parameters were recorded and compared in 74 preterm and 30 full-term infants. The study was performed to find out changes of BAEP parameters in preterm infants and to assess functional maturation of the auditory pathway with respect to gestational age. According to the study, there were significantly prolonged BAEP parameters among preterm population. Group 1 preterm infants, with prolonged wave V and I-V interwave latency, showed immaturity of both sided central auditory pathway, especially around inferior colliculus (brainstem). Group 2 infants, whose right wave I and V were delayed, but not I-V interwave latency, suggested right sided immaturity of peripheral pathway from middle ear to cochlea and distal part of auditory nerve (pathology of external ear was excluded). In Group 3, all the wave latencies were within normal limit. Among 74 cases, 24 infants (32.43%) were found to have absent waves. Maximum numbers of absent waves (38.89%) were present in Group 3.

The BAEPs can be recorded in premature infants as early as 26 weeks of gestational age [17,18]. The absolute latencies of BAEP waves and their inter-peak latencies progressively decrease over the course of neurological development [19].

Preterm babies had prolonged absolute latency of wave I {2.02(0.3) Ms}, wave V {6.87(0.48) mS} and interwave latency of I–V {4.85(0.43) mS} compared to normal term babies. These observations reflect a delayed maturation of peripheral and central auditory pathway and support the findings of others, that waveform latencies are delayed due to prematurity itself [20,21].

Prolongation of absolute latencies and interwave latency occurs possibly due to delay in electrical conduction as the process of myelination is still in progress and auditory pathway through brainstem is still immature; suggesting that the degree of myelination, stage of development of nerve fibers of auditory pathways, reduced axon diameter, and immaturity in synaptic function, affect the latencies of waves [20-22].

Similar findings were observed by Roopkala MS et al., Jiang ZD et al., Pasman JW et al., Ken dror A et al., Morgon A et al., and Lina Grenade G et al., [23-28]. In the study by Casali RL and Santos MFC, absolute latencies of waves I, III, and V of preterm infants were also prolonged [29]. In the study of Lakhhsmi T et al., preterm infants had prolonged latency of wave V, which reflects immaturity of the auditory system [22]. Though, in the study by Kilic I et al., there was no difference in absolute latencies and interpeak latencies between term and preterm babies [15]. In the study by Marlow ES et al., preterm infants with sensorineural hearing loss had longer periods of intubation, ventilation, oxygen treatment, and acidosis, and more frequent treatment with dopamine or furosemide [16].

There is an inverse correlation between gestational age and absolute latencies with increasing gestational age, and hence the maturation of central auditory system occurs gradually with continuous decrease of absolute latencies of all the waves in infants. Wave V shows a greater change with age than does wave I, and thus the I-V interpeak latency also decreases with age. This decrease is related to the progressive myelination of central nervous system structure, increase in axonal diameter, the improvement in synchrony of neural activity, establishment of effective structural connections, and increased function of the synapses. Studies report a systematic decrease in latency as a function of increasing age [21,25,30]. The present study also showed similar findings. Group 1 preterm infants whose mean gestational age was 27.85 (0.54) weeks, showed prolonged wave V and I-V interwave latency in comparison with control group and prolonged left sided I-V interwave latency, in comparison with Group 3 preterm infants whose mean gestational age was higher i.e., 34.78(1.44) weeks. However, Despland PA and Galambos R, and Montandon PB et al., showed the earlier maturation of the peripheral nervous system relative to the later maturing central auditory pathway [30,31]. In present study, among Group 1 preterm infants, this view was supported, as no prolongation of wave I signified earlier maturation of peripheral auditory system in comparison with central auditory pathway, which was still immature. But, the view was contradicted among Group 2, where central pathway was matured earlier than peripheral pathway. This may be due to transient perinatal conductive loss which occurs as a result of temporary presence of middle ear fluid up to of 3-5 months or due to immaturity of cochlea or distal part of auditory nerve [32].

In every group absent waves were present. It occurs due to non uniform delay of neuronal activity in peripheral and central auditory pathway or if the electrical signals are desynchronised, the summation may not produce a recognisable wave, so absent wave results. Same patho-physiological process can cause either delay or absence of a BAEP peak. They both indicate dysfunction but not necessarily complete loss of activity in a part of the infratentorial auditory pathways. Again, only peripheral auditory dysfunction is sufficient to cause complete absence of BAEP waves [14]. In present study, absent waves were present in 32.43%, among 74 cases. In Group 1, 26.92%; in Group 2, 33.33% and in Group 3, 38.89% preterm infants showed absent waves.

In the study of Casali R and Santos MFC, there were no significant prolongation of wave I, III, V and I-V interwave latency between left and right ear [29]. A statistically significant difference was found only in the I-III interpeak latency, where left ear values were delayed in comparison to the right ear. But, interpretation of a prolonged I-III or III-V interpeak interval when the I-V interpeak interval is normal is less clear. Guilhoto LMFF et al., and Sleifer P et al., also showed no absolute and interpeak latency difference between two ears [20,21]. In contrary, according to present study, right sided wave I,V,I-V intewave latency were significantly prolonged.

LIMITATION

The major limitation of the study was that it was cross-sectional. A follow up study with a larger sample would be beneficial to know about the gradual changes occurring in the course of postnatal period and also to study the duration when the preterm brain maturation probably catches up with that of the full term. Information regarding other confounding factors like, maternal age during pregnancy, other antenatal history, family history, drug history, etc was also inadequate. Equal number of control group could not be taken and it was limitation of present study.

CONCLUSION

These preterm infants had immaturity of the peripheral as well as central auditory pathway more so in the right side than the left side. According to gestational age, extremely preterm infants showed more immaturity of central auditory pathway. Late preterm i.e., group 3 showed maturity of auditory pathway just like full term infants. Yet they had maximum number of absent waves, suggestive of abnormality in auditory transmission. So, the finding of this study gave us a preliminary idea about BAEP changes among preterm infants. Based on which proper follow up at six months, 1 year, and 2 years is necessary to see whether these alterations are temporary or permanent. Prompt management should be initiated in persistent changes, as early as possible, to improve hearing ability and linguistic development of the child.

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