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Brainstem Auditory Evoked Potential In Neonatal Hyperbilirubinaemia And Its Relation With Different Levels of Bilirubin

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Abstract
Background*: Hyperbilirubinemia , one of the commonest complaints of neonatal life, is toxic to the auditory pathways . Brainstem evoked response audiometry (BERA), which assess Brainstem auditory evoked potential(BAEP), is a non-invasive and objective way of evaluating functional integrity of auditory pathway .*
Aims :*The study was done to observe changes of BAEP parameters in neonatal hyperbilirubinaemic infants and to analyze relation between damage of auditory pathway as indicated by BAEP changes with the level of bilirubin.*
Methods *:This cross sectional study was done in Eastern region of India. One hundred eight neonatal hyperbilirubinaemic infants and thirty normal infants were included .The cases were divided into two subgroups according to level of bilirubin in neonatal period -Group 1(15-20mg/dl); Group 2(>20mg/dl) .Statistical analysis was done by Student t test,*
Results *:Cases had prolonged wave V latency and I–V Interwave latency in both sides and delayed wave I in right side (P<0.05). Absent waves were present in 22 infants out of 108 subjects.In group 1, wave V &I-V latency were prolonged in right side. Both sided prolongation of wave I & wave V were present in group 2 along with prolonged Wave I in right side. Right I,V,I-V and Left I,V,I-V were prolonged in group 2 than group*
Conclusions: *Neonatal hyperbilirubinaemic infants had bilirubin mediated toxicity in auditory pathway. Group 2 infants were presented with more damage in comparison with group 1. Absent waves were present in both the groups suggestive of dysfunction of auditory pathway but exact location of pathology was uncertain.*
Keywords *: BAEP, Neonatal Hyperbilirubinaemia, Bilirubin level, Neurotoxicity.*

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I. Introduction

The auditory pathway is one of the most susceptable parts of the central nervous system to noxious agents like increased level of bilirubin. One of the commonest high risk factors in neonates is hyperbilirubinaemia, which clinically manifests as jaundice [1,2] Jaundice is seen in 60% of term neonate at birth[3]. Auditory neuropathy is a common sequele of severe neonatal hyperbilirubinaemia[4,5,6]. If not controlled, this can lead to hyperbilirubinaemic encephalopathy or neonatal death. Moreover surviving infants are at high risk of neurological damages like cerebral palsy, epilepsy, sensorineural hearing loss [7, 8].The hyperbilirubinaemia induced dysfunction includes multiple abnormalities; which is dependent on acute or chronic exposure of CNS to bilirubin. In the spectrum,there are kernicterus, acute bilirubin encephalopathy, and isolated neural pathway dysfunction [9]. Up to 40 percent of hyperbilirubinaemic neonates are at risk of hearing loss [10]. The sensitivity of the auditory system to bilirubin has been previously documented . Many researchers reported the relationship between hyperbilirubinaemia and damage to the auditory system [11,12,13]. Hyperbilirubinaemia affects auditory brainstem nuclei and inferior colliculus [14]. Abnormalities in spiral ganglion neurons and myelinated auditory fibers are also reported [15]. In different audiological studies among children with high serum bilirubin level (>20 mg/dl) showed auditory dysfunction in 17-87% of cases [10, 16-19].The damage to the auditory system has long-term as well as permanent effects, since language development is dependent on auditory function [20]. Early diagnosis depends on systematic hearing screening. There is no objective method other than Brainstem Evoked Response Audiometry (BERA) to evaluate the toxic effects of high bilirubin on CNS. Evoked potentials are non invasive tools to evaluate the integrity and functional maturation of the afferent pathways of nervous system. BERA ,which records Brainstem Auditory Eviked

Potential(BAEP) is an useful tool in detecting the acute neurotoxicity of bilirubin on the auditory pathway [21]. It is based on recording the electrical activity of the auditory system that occurs in response to an appropriate acoustic stimulus [22]. The BAEP waveform in neonates and infants comprises of 3 identifiable waves (I, III, and V). Many studies have shown abnormal BAEP , in the form of, an increase in the wave's latency in infants with hyperbilirubinaemia. The latency delay of different wave peaks, inter wave latency delay have been established by various studies in infants [23,24]. BAEP abnormality in these infants is an indicator of bilirubin ototoxicity [25,26,27]. On the other hand, another category of studies did not find any abnormalities in these groups of patients [21,28,29,30] . This creates a milieu upon which the present study was based. The research hypothesis was , BAEP abnormalities were present in all infants with neonatal hyperbilirubinamia.

This cross-sectional study evaluated, BAEP among neonatal hyperbilirubinaemic infants in comparison with normal infants and relation of bilirubin level in BAEP parameters. The study aimed to document whether there were BAEP changes among the infants with H/O neonatal hyperbilirubinaemia and whether auditory pathway damage, reflected by BAEP changes were related with level of bilirubin. This may indicate, presence of neurotoxicity, for which early diagnosis and treatment are crucial for improving linguistic development and prognosis of these infants.

II. Materials And Methods

BAEP data of 108 neonatal hyperbilirubinaemic infants were compared with 30 normal infants, taken as contol group. These infants with H/O neonatal hyperbilirubinaemia were further divided into two groups according to their bilirubin level .They were compared with control population and intragroup comparison was done. These groups were , Group 1- consists of infants with history of bilirubin level(15-20mg/dl) in neonatal period Group 2- consists of infants with history of bilirubin level(>20mg/dl) in neonatal period.The infants who were born with neonatal hyperbilirubinaemia (>15 mg/dl) and got admitted in Neonatal Intensive Care Unit were advised for BERA[Brainstem Evoked Response Audiometry] (to evaluate BAEP abnormalities). Both inborn and outborn infants at R.G.Kar Medical College,Kolkata, were included. Along with them, infants , who were born with neonatal hyperbilirubinaemia and attended to sick baby clinic of Out Patient Department(OPD),were also advised for the same test in Applied Physiology Lab at Department of Physiology at R.G.Kar Medical College within 3 months of their date of birth[31,32]. Control group was selected from Well Baby Clinic of pediatrics OPD, R.G.Kar Medical College.The study was conducted for one year from March 2015 to March 2016, in Department of Physiology in collaboration with Department of Pediatric Medicine of R.G.Kar Medical College. The study was approved by the Institutional Ethics Committee,R.G.Kar Medical College, Kolkata. Severely ill infants or Infants, born as Preterm neonate or low birth weight neonate(birth wt. <2500gm and gestational age <37 weeks),craniofacial anomalies, chromosomal disorders, intrauterine infections, birth trauma, metabolic disorders or intracranial infection were excluded .Infants with H/O recent Upper Respiratory Tract Infection (URTI)or any pathology in external ear were also excluded. Informed written consent was taken from the parents or guardians of all infants.

III. Procedure

Brainstem Evoked Response Audiometry (BERA) was recorded with the help of the machine Neuro-MEP4,Ivanovo, Russia . At first, parents were interviewed to fill in the study protocol and to gather a clinical history. External ear assessment , was carried out and findings were documented. Parents or guardians of the infants were explained about the test and asked to apply shampoo at the day before examination . They were told to come on the very day along with infant and after arriving, proper consent form were being explained and signed . They were also instructed to wake the infants up in early morning of the test day , so that infants remained asleep during the whole recording time as in order to exclude biologically derived noise due to muscle activity . Calm and quiet awake infants were also accepted and included for this test. It was done in quiet and cool surrounding . Scalp and forehead were cleaned with Nuprep cleaning gel for electrode placement.The surface electrodes were used for recording Brainstem Auditory Evoked Potential. The silver cup electrodes were fixed over scalp with electrolyte paste. The electrode impedance was less than 5 kohm. The electrodes were placed at , vertex(Cz) and at both mastoids as per International 10-20 system . The mastoids, ipsilateral and contralateral to the stimulated ear are labeled Ai and Ac respectively. The ground electrode (Fz) were placed over forehead(31).Mono phasic square pulse acoustic clicks were used at 11.1 pulse/sec. Click duration was 0.1 ms. Rarefaction clicks were used with 0.5 micro-volt sensitivity and 1 ms/Div sweep speed . BAEP recording was done by applying 70 dB stimulus intensity in ipsilateral ear and 40 dB lower than stimulus intensity was used as masking noise in contralateral ear. Filter setting was adjusted between 100Hz-3000Hz. Two thousand evoked responses were averaged 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 brainstem auditory evoked potential were compared between the study group and control group to assess any significant difference

of wave latencies. When BAEP parameters of cases were prolonged in respect to these normal range of values, derived from control group, or when BAEP waves are absent, both considered as abnormal.

IV. Statistical Analysis

At 70 dB intensity BAEP changes of 108 infants with H/O neonatal hyperbilirubinaemia were compared with 30 normal infants taken as control group. To compare data of main group as well as subgroups with control population, and to compare data among two sub groups Student's t-test was applied and statistical analysis was done with Graph Pad Quick Calc software, California, USA . P value <0.05 – considered as Statistically Significant.

V. Results

This cross sectional study consisted of 108 infants with H/O neonatal hyperbilirubinaemia . Sex and Postnatal age wise they were similar with 30 full term infants, taken as control. BAEP parameters, latencies of wave I, wave III, wave V, and I-V interwave latency were recorded and compared between control group and total case population as well as subgroups of cases . The result of the study was represented below in the form of tables.

Table1: Comparison of BAEP parameters in left ear between cases and controls

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	90 out of 108	1.96(.25)	1.9(0.14)	0.21
WaveIII	90 out of 108	4.59(.4)	4.57(0.28)	0.8
WaveV	90 out of 108	6.91(.51)	6.63(0.2)	**0.004***
I-V Interwave Latency	90 out of 108	4.94(.48)	4.7(0.17)	**0.009***

mS-milisecond * statistically significant

Table2: Comparison of BAEP parameters in right ear between cases and controls

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	89 out of 108	2.02(0.28)	1.9(0.14)	**0.03***
WaveIII	89 out of 108	4.63(0.39)	4.54(0.36)	0.27
WaveV	89 out of 108	7.01(0.43)	6.58(0.17)	**0.0001***
I-V Interwave Latency	89 out of 108	4.99(0.4)	4.68(0.16)	**0.0001***

mS-milisecond * statistically significant

According to Table:1 ,waveV, I-V interwave latency were statistically significantly prolonged between cases and controls in left ear whereas according to Table: 2, wave I, wave V, I-V interwave latencies were statistically significantly prolonged in right ear of the cases . This was suggestive of neurotoxic damage of central auditory pathway in left side and both central and peripheral auditory pathway damage in right side.

Table3: Comparison of BAEP parameters in left ear between Group1(n=52) infants and controls(n=30)

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	52 out of 60	1.95(0.23)	1.9(0.14)	0.28
WaveIII	52 out of 60	4.62(0.41)	4.57(0.28)	0.56
WaveV	52 out of 60	6.74(0.44)	6.63(0.2)	0.2
I-V Interwave Latency	52 out of 60	4.79(0.39)	4.7(0.17)	0.23

mS-milisecond

Table4: Comparison of BAEP parameters in right ear between Group1(n=50) infants and controls(n=30)

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	50 out of 60	1.96(0.23)	1.9(0.14)	0.2
WaveIII	50 out of 60	4.65(0.35)	4.54(0.36)	0.18
WaveV	50 out of 60	6.87(0.39)	6.58(0.17)	**0.0002***
I-V Interwave Latency	50 out of 60	4.91(0.39)	4.68(0.16)	**0.003***

mS-milisecond * statistically significant

According to Table:3 ,there were no statistically significant difference between cases and controls in respect to all 4 parameters in left ear whereas according to Table: 4, wave V, I-V interwave latencies were statistically significantly prolonged in right ear of the cases in respect to control population. This was suggestive of neurotoxic damage of central auditory pathway in right side.

Table5: Comparison of BAEP parameters in left ear between Group2 (n=38) infants and controls(n=30)

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	38 out of 48	1.99(0.28)	1.9(0.14)	0.11
WaveIII	38 out of 48	4.56(0.4)	4.57(0.28)	0.91
WaveV	38 out of 48	7.14(0.5)	6.63(0.2)	**0.0001***
I-V Interwave Latency	38 out of 48	5.15(0.52)	4.7(0.17)	**0.0001***

mS-milisecond * statistically significant

Table6: Comparison of BAEP parameters in right ear between Group2(n=39) infants and controls(n=30)

BAEP parameters Latency(mS)	Wave present in cases	Case Mean(SD)	Control Mean (SD)	P value
WaveI	39 out of 48	2.11(0.32)	1.9(0.14)	**0.001***
WaveIII	39 out of 48	4.61(0.44)	4.54(0.36)	0.48
WaveV	39 out of 48	7.2(0.41)	6.58(0.17)	**0.0001***
I-V Interwave Latency	39 out of 48	5.09(0.39)	4.68(0.16)	**0.0001***

According to Table:5 ,waveV, I-V interwave latencies were statistically significantly prolonged between cases and controls in left ear whereas according to Table: 6, wave I, wave V, I-V interwave latencies were statistically significantly prolonged in right ear of the cases . This was suggestive of neurotoxic damage of central auditory pathway in left side and both central and peripheral auditory pathway damage in right sideAll these neonatal hyperbilirubinaemic infants were divided into two groups according to level of bilirubin. Individual result of each group was demonstrated and compared below.

Table7:Intragroup comparison of all BAEP parameters

BAEP parameters	Group1 Mean(SD)	Group 2 Mean(SD)	P Value
Left I	1.95(0.23)	1.99(0.28)	0.46
Right I	1.96(0.23)	2.11(0.32)	**0.01***
Left III	4.62(0.41)	4.56(0.4)	0.49
Right III	4.65(0.35)	4.61(0.44)	0.63
Left V	6.74(0.44)	7.14(0.5)	**0.0001***
Right V	6.87(0.39)	7.2(0.41)	**0.0002***
Left I-V	4.79(0.39)	5.15(0.52)	**0.0003***
Right I-V	4.91(0.39)	5.09(0.39)	**0.03***

* statistically significant

Table: 7 shows that in both the ears, wave V and I-V interwave latencies were statistically significantly prolonged and in right ear wave I latency was also statistically significantly prolonged among Group 2 infants, in comparison with Group 1 population. This suggests significant neurotoxic damage of central auditory pathway of both ear and significant peripheral neurotoxic damage of right ear were present in higher bilirubin group .

VI. Discussion

BAEP parameters were recorded and compared in 108 neonatal hyperbilirubinaemic infants and 30 normal infants. The study was performed to find out changes of BAEP parameters in cases and to assess functional integrity of the auditory pathway with respect to level of bilirubin . According to the study there was significantly prolonged BAEP parameters among case population. Group 1 preterm infants, with prolonged right sided wave V & I-V interwave latency, showed bilirubin mediated damage of central auditory pathway of right ear, from proximal auditory nerve to inferior colliculus(brainstem). Group 2 infants, whose right wave I , V and I-V interwave latency were delayed, suggested right sided toxin mediated damage of peripheral pathway i.e from middle ear to cochlea and distal part of auditory nerve(Pathology of external ear was excluded) as well as central pathway.Again, in Group 2,left side, wave V & I-V interwave latency,were prolonged and suggestive of neurotoxic damage of central pathway. In intragroup comparison, wave V, I-V interwave latency of both ear and wave I latency of right ear were significantly prolonged in group 2 infants. This means more damage occurs

in both sided central pathway and right sided peripheral pathway in group 2 infants.Among 108 cases, 22infants(20.37%), were found to have absent wavesThe most sensitive area in the auditory system seems to be , the brainstem auditory nuclei. Bilirubin encephalopathy affects Superior olive, Lateral leminiscus & inferior colliculus[33]. The brainstem auditory evoked potential (BAEP) , is absent or abnormal, reflecting damage to the auditory nerve (wave I) and/or, more likely, auditory brainstem nuclei (waves III and V)[34Many workers had presented the relation between hyperbilirubinaemia and BAEP abnormalities.Lenhardt ML, McArtor R, Bryant B. [35] performed BAEP test in 10 neonates with hyperbilirubinemia soon after birth and repeated the test in five of these children. They compared the results with a control group consisting of 10 neonates with normal serum bilirubin levels, and found that absolute wave III and wave V latencies were higher in the study group, compared with the control group; Nakamura et al.[36] carried out BAEP testing in auditory assessments of 56 hyperbilirubinemic neonates and 24 neonates with no jaundice to assess whether bilirubin could cause early ototoxicity. Absolute Wave I latencies were increased compared with the control group.Sharma et al.[23] carried out BAEP testing for the auditory assessment of 30 jaundiced neonates soon after birth and after 2 to 4 months. The mean wave absolute latencies and their interpeaks were prolonged in jaundiced neonates compared with controls, suggesting early bilirubin-induced encephalopathy. BAEP alterations persisted in 23.3% of these cases in follow up, demonstrating the importance of this test for early detection of hearing loss.All these cause-effect studies were prolonged follow-up studies, where as this present study was a cross-sectional one. Though, there were also several studies , which were done in one time & demonstrated hyperbilirubinaemia , as a causative factor of Auditory abnormalities and BAEP changes.Salehi et al[37] showed , the BAEP findings among 42 term infants with neonatal hyperbilirubinaemia, were, significant increase in the absolute latencies of waves III and V, and I-III and I-V inter-peak latencies of the sample group compared to the control group in both ears.Camargo da Silva et al showed that BAEP findings of 25 hyperbilirubinaemic infants were , discretely prolonged wave V in right ear & I-V interwave latency in left ear.[38] Mukhopadhyay et al showed, BERA was abnormal in 76% cases among 25 newborn of >35 weeks with TSB[Total Serum Bilirubin]>20mg/dl,getting exchange transfusion. BERA test was done at 3monthes of age.[39]Other co-workers like Boo NB et al, Baradaranfar MH et al[16,17] also showed abnormalities of AuditorEvokedPotential in hyperbilirubinaemic infants .Where as Chen et al[21] stated that, there was no significant association between the maximum totalserum bilirubin and brainstem auditory evoked potentialsThe present study also dealt with BAEP abnormalities in respect to highest level of bilirubin at neonatal period. There were two groups, Group 1(Highest level of bilirubin 15-20 mg/dl) & Group 2 (Highest level of bilirubin >20 mg/dl). Other than absence of all waves ,when these groups were compared with control population, the BAEP prolongations were present in both the groups,and more neurotoxis damage was found in higher bilirubin group(group2),when intragroup comparison was made.

In similar studies, like Aggarwal et al,[24], 30 hyperbilirubinaemic cases were divided into three groups: (i) Group A - Serum bilirubin 15-20 mg/dl; Group B - Serum bilirubin 21-25 mg/dl; and Group C - Serum bilirubin >25 mg/dl. Abnormality in brainstem auditory evoked response correlated significantly with bilirubin level. One out of 9 (11.1%) neonates in Group A, 10 out of 15 (66.6%) neonates in Group B and all the 6 neonates in Group-C had bilateral abnormal responses on initial BAER denoting brainstem dysfunction In contrary,Wong et al[30]showed that 99 full term hyperbilirubinaemic infants divided into three groups: group 1, moderate hyperbilirubinemia (n = 30; mean maximum total serum bilirubin = 320.7 µmol/L or 18.9 mg%); group 2, severe hyperbilirubinemia (n = 63; mean maximum total serum bilirubin = 369.0 µmol/L or 21.7 mg%); and group 3, super hyperbilirubinemia (n = 6; mean maximum total serum bilirubin = 457.2 µmol/L or 26.9 mg%),had no significant correlation between maximum total serum bilirubin, and total serum bilirubin at discharge with an abnormal brainstem auditory evoked potential. There was no significant difference in the rate of brainstem auditory evoked potential abnormalities betweenthe three groups: moderate (10%), severe (7.9%), and super (16.7%).In the present study, there were two types of findings which were statistically significant One finding was, latency of wave V & I-V interwave latency were significantly delayed whereas wave I latency was WNL. As I-V interwave latency is related to central auditory pathway transmission time(CTT), this particular finding suggested, delayed central transmission time & excess bilirubin mediated neurotoxic damage of myelination in central auditory pathway.[31]Another finding was, latency of wave I & wave V and I-V interwave latency are significantly delayed . Prolongation of waveV and I-V interwave latency means damage of central pathway. But wave I latency is related to peripheral auditory pathway transmission time (PTT), this particular finding suggests, delayed peripheral transmission time & excess bilirubin mediated neurotoxic damage at peripheral part.[31]. But peripheral part includes external ear, middle ear & inner ear (cochlea). There is no evidence of bilirubin mediated damage of external or middle ear, though high level bilirubin may affect cochlea. A study done by da Silva et al(38), showed that in hyperbilirubinaemic infants cochlea may be affected & this fact was based on the data derived from Otoacoustic emission and BERA. This same BAEP finding is also present when pathology lies in distal auditory nerve.A study done by Shapiro(34), stated that In the auditory system, bilirubin does not appear to affect either inner or outer hair cells, although it may affect the cell bodies

of the auditory nerve in the spiral ganglia. The mechanical structure of the inner ear is assessed clinically with otoacoustic emissions (OAEs), and the outer hair cells of the inner ear are tested with cochlear microphonic responses (CMs). Both OAEs and CMs are normal in neonates with bilirubin-induced injury. The brainstem auditory evoked potential (BAEP) , reflects damage to the auditory nerve and prolongation of wave I. So, in this present study, the finding was suggestive of bilirubin mediated damage either in cochlea or in auditory nerve. For the exact location, OAE needed to be done.

In every group absent waves were present .It happens due to non uniform delay of neuronal activity in auditory pathway or if the electrical signals are desynchronized, the summation may not produce a recognizable wave, so absent wave results. Same patho physiological process can cause either prolongation or absence of a BAEP peak. They both indicate dysfunction but not necessarily complete loss of function in a part of the infratentorial auditory pathways. Again, only peripheral auditory dysfunction is sufficient to cause complete absence of BAEP waves(31).In present study, absent waves were present in 20.37%, among 108 cases. In Group1, 16.67% ; In group2 ,25% infants showed absent waves.There were some limitations of this present study. This one was a cross-sectional study, though to observe the actual effect of high bilirubin in auditory pathway, follow up study is always better. In many long term follow up studies[6,24] or studies done before & after therapy[23,24,36], reversible BAEP abnormalities were suggestive of transient nature of bilirubin damage among a good percentage of total population. The BERA test could not be done on hyperbilirubinaemic neonate before initiation of any therapy due to various constraints. n the present study total serum bilirubin was used though level of unbound circulating bilirubin in plasma or The ratio of total serum bilirubin (in milligrams per deciliter) to serum albumin (in grams per deciliter) can predict bilirubin-induced CNS injury more accurately but data was unavailable. During BERA test, this was always better to use insert earphone for providing click sound, but in present study acoustically shielded earphones were used as insert earphone was very delicate instrument & had to be handled very carefuly. Information regarding other confounding factors like ,maternal age during pregnancy, family history, etc were also inadequate

VII. Conclusion

Severe neonatal hyperbilirubinaemia is particularly toxic for the auditory pathway. The purpose of the study was to find out BAEP changes among a group of infants having H/O neonatal hyperbilirubinaemia . This present study clearly demonstrated that , there were significant BAEP changes among infants with neonatal hyperbilirubinaemia. .Statisticaly more abnormalities were present in higher bilirubin group . So, in conclusion, most of the BAEP abnormalities were suggestive of retrocochlear damage done by toxic level of bilirubin. Other BAEP finding showed possibility of cochlear involvement too.Results of this study underline the importance of auditory evoked potentials in evaluating the infants' auditory system. BERA can be an efficient tool for monitoring the auditory brainstem pathway in infants who are at risk of neurotoxicity. Diagnosing the earliest stages of auditory damage caused by high levels of bilirubin is key at a stage where lasting central effects may be preventable.Furthermore, this study gave an idea based on which, further study can be done proper follow up, so that interpretations of the results will be more conclusive and that will be highly informative in respect to initiation of treatment or rehabilitative measures at proper time.

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