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Insights from a single-center study: Cessation of Anti-seizure Medication in Neonatal seizures

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ABSTRACT

Seizure susceptibility is greatest during the neonatal period of life. Early termination of these seizures is recommended by studies to prevent unfavorable long-term outcomes. We investigated the factors for ceasing anti-seizure medication in infants who experienced seizures during the neonatal period. This retrospective, single-center, descriptive study was conducted in tertiary medical center between December 2020 and February 2023, and 157 neonates were recruited. The possible confounding factors identified by the univariate analysis and the multivariate studies' logistic regression analysis was used to identify independent predictors for cease anti-seizure medication (ASM) at the infancy. The sensitivity, specificity, positive, and negative predictive values were displayed when a significant cut-off value was found by Receiver Operating Characteristic curve analysis. Having a younger age at the first seizure (younger than 45.5 hours), using poly-therapy at the neonatal intensive care unit discharge, the presence of structural abnormalities in the brain related to the etiology of seizures, increased spike activity and burst suppression in EEG records decreased the likelihood of cease ASM before 12 months. The probability of cease ASM before 12 months was increased with a normal EEG. Our findings support that EEG and neuroimaging findings are the key factors for making decisions in the follow-up of infants with neonatal seizures. The potential long-term negative effects of ASM consumption can be reduced by discontinuing its use, when EEG results are normal. However, the etiology of structural abnormalities and the use of poly-therapy at the NICU discharge require caution in making early ASM discontinuation decisions.

Keywords: Neonate, seizure, early onset epilepsy, anti-seizure medication, EEG

Introduction

During the neonatal stage of human development, individuals are particularly susceptible to seizures. Studies suggest that it's beneficial to promptly end these seizures to mitigate adverse long-term consequences. Research has extensively documented the impact of neonatal seizures on neurodevelopment, revealing limitations in both physical and cognitive abilities, along with an increased risk of behavioral disorders such as attention-deficit/hyperactivity disorder and autism, as well as the onset of epilepsy following the neonatal period (1). Acute provoked seizures and early-onset epilepsies are distinct seizure types, each characterized by unique underlying causes, clinical presentations, and long-term prognoses. Neonatal seizures, which are often acute provoked, typically resolve within 72 hours (2). Conversely, neonatal epilepsy syndromes, although rare, are frequently associated with genetic factors, necessitating prolonged administration of anti-seizure medication (ASM) (3).

The guidelines from the International League Against Epilepsy commonly advocate for phenobarbital as the initial treatment option for neonatal seizures (4). However, concerns arise regarding phenobarbital's impact on immature brain development, with studies noting impaired synaptic maturation and widespread neuronal apoptosis in immature rat brains following phenobarbital exposure (5, 6). In cases where neonates do not respond to phenobarbital as the first-line ASM, secondary interventions like phenytoin, levetiracetam, midazolam, or lidocaine may be considered. Recent updates in neonatal seizure management guidelines have incorporated third-generation ASMs like levetiracetam due to their proven efficacy and safety (7). Nonetheless, there remains a gap in understanding the long-

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term effects of these newer medications on immature brains (8). Consequently, while delaying treatment for neonatal seizures can lead to lasting impairments, prolonged use of ASMs may also have adverse consequences on overall outcomes, as previous research suggests (5). Most clinical studies have focused on acute provoked seizures, but there is increasing evidence supporting the adoption of more tailored pharmacological techniques for selective genetic epilepsies, which continue to advance (9).

The primary objective is to discontinue the use of ASMs in neonates as soon as seizures are effectively controlled, without delay during the neonatal period (10, 11). While there is a consensus on the importance of stopping medication at the earliest possible time, there is still uncertainty regarding the precise timeframe or guidelines for cessation. The duration of anti-seizure drug administration for neonatal seizures differs based on individual physician's clinical judgment and considerations from parents (12).

Our main objective was to investigate the determinant factors related to ceasing ASM for infants experiencing seizures in the neonatal period, aiming to tailor the treatment duration for neonatal seizures.

Materials and Methods

Study Cohort: This was a retrospective, observational, single-center study of neonates' data with acute symptomatic seizures between December 2020 and February 2023 conducted at a tertiary institution. A total of 157 neonates who were treated at level IV neonatal intensive care unit (NICU) with acute symptomatic seizures were recruited to determine the factors related to ASM treatment cessation in infancy at least follow-up 2 years. A total of 157 neonates were recruited to determine the factors related to ceasing ASM treatment in infants at a follow-up 2 years. According to the International League Against Epilepsy classification of neonatal seizures and their etiology, patients who were diagnosed with such seizures and received ASM within the first 28 days of life were followed until their ASM was ceased after they were discharged from the NICU (13).

Infants are defined as children aged younger than 12 months. During this stage of neuronal development, the central nervous system is more susceptible to the harmful effects of external factors. Consequently, we have planned an evaluation of the study's initial 12-month follow-up results for our group. Afterwards, the infants were divided into two groups: the first group consisted of infants who continued to receive ASM treatment after 12 months of age (referred to as "infants still on ASM after 12 months", n=69); the second group consisted of infants who had stopped ASM treatment before 12 months of age (referred to as "infants who had ceased ASM before 12 months", n=88). Using these sample sizes, we estimated over 80% power to detect a difference of 15% in the duration of treatment between the groups at a 2-sided α level of 0.05. The study was approved by the local ethics committee.

The study included all infants who were diagnosed with acute provoked seizures based on clinical observation and confirmed by conventional electroencephalography (cEEG). The inclusion criteria were as follows: (1) Neonate with an amplitude integrated EEG (aEEG)-confirmed seizure or (2) neonate had administered ASM to address suspected seizure-related clinical events, based on supporting clinical history and event features, and (3) the seizures were triggered by an acute symptomatic factor, such as hypoxic-ischemic encephalopathy, ischemic stroke, intracranial hemorrhage, or another acute brain injury. Neonates with abnormal paroxysmal events that weren't determined to be seizures by cEEG, aEEG and video records, who stopped medications due to their parents' decisions, with missing hospital records, and delivered from pregnancies by assisted reproductive techniques were not enrolled.

Clinical Variables: Gender, birth weight, age at first seizure, gestational age, seizures' etiology, seizure type, number of seizures (per day), family history of epilepsy, ASM protocol (monotherapy/poly-therapy) at the time of discharge, cEEG, and neuroimaging results were confounder factors of decision for treatment duration. The neonatologists caring for each neonate made decisions on their own for treating acute provoked seizures in neonates, in terms of the choice of medication. The duration of therapy was consulted by a pediatric neurologist based on the confounding factors. The primary requirements for ceasing ASM, the following criteria should be met: (1) An EEG that shows consistent characteristics for the gestational age, (2) no structural abnormalities which damage to the cerebral cortex, documented by neuroimaging, (3) a seizure-free period of at least one month. A gradual dose reduction of 25% should be

implemented as part of the medication withdrawal regimen.

EEG and Neuroimaging Classification: The cEEG data of all 157 neonates was obtained from 18 channels, with scalp electrodes positioned in accordance with the 10–20 system, in accordance with criteria published by the American Clinical Neurophysiology Society (14). The recording spanned at least 30 minutes of sleep trace. The cEEGs were evaluated and categorized as either normal or abnormal, with abnormal results demonstrating focal epileptiform activity, irregular background activity, increased spike activity, and burst suppression.

All the infants had a cranial magnetic resonance imaging (MRI) to detect any structural anomalies. The results were classified as normal or abnormal, the latter pointing to the presence of intraventricular hemorrhage, intracerebral hemorrhage, ischemia, periventricular leukomalacia, cystic encephalomalacia, white matter abnormalities of insignificance, and corpus callosum hypoplasia.

Statistical analysis: Statistical analysis was performed using SPSS software version 25. The normality of the variables was examined by visual methods such as histograms and probability plots, as well as analytical techniques like the Kolmogorov-Simirnov test. Descriptive analyses were presented with tables of frequencies (for the ordinal variables), and medians and interquartile range (IQR) (for the non-normally distributed and ordinal variables). The univariate analysis to identify variables associated with infants' likelihood of stopping ASM before 12 months were investigated using Fisher exact test, Student's t test, and Mann-Whitney U test, where appropriate. In order to find independent predictors for cease ASM before 12 months of age, the potential components found by univariate analysis were subsequently entered into logistic regression analysis for the multivariate analyses. To evaluate the model's fit, Hosmer-Lemeshow goodness of fit statistics were employed. Receiver Operating Characteristic (ROC) curve analysis is used to examine the factors that contributed to the delay in stopping ASM before a 12-month period. The sensitivity, specificity, positive, and negative predictive values were displayed when a significant cut-off value was found. A 5% type-I error threshold was applied when assessing the area under the curve (AUC) in order to accept a statistically significant predictive value for the test variables.

Results

The study consisted of 157 infants with ASM treatment due to experiencing seizures in the neonatal period were enrolled. The average gestational age of the patients was 37.2±3.6 weeks, the average birth weight was 2930±869.8 grams, and 84 of the neonates were boys.

All participants were evaluated based on their demographic and clinical characteristics to identify relevant factors associated with the ceasing of ASM. Mean duration of ASM was found 6.6±4.04 months. A comprehensive summary of these factors can be found in Table 1.

By comparing the groups, age at first seizure, family history of epilepsy, duration of ASM, etiology of neonatal seizures (such as hypoxic ischemic encephalopathy, structural abnormality of the brain, idiopathic), therapy protocol (poly-therapy), the results of EEG (normal EEG pattern, irregular increased spike activity, background activity, burst suppression) and cranial MRI (Normal MRI), and type of ASM used were found to be statistically significant factors related to withdrawal of ASM. In Table 2, the data is summarized by comparing the 2 groups (Infants still on ASM after 12 months, infants had withdrawn of ASM before 12 months).

We utilized univariate logistic regression analysis to identify factors that related to more than 12 months of ASM usage in infants with neonatal seizures. Variables with a P-value less than 0.25, including age at first seizure, family history of epilepsy, etiology, treatment protocol, abnormal findings on EEG, and neuroimaging, were subsequently included in the multivariate analysis. Determinants related to the cessation of ASM were evaluated using logistic regression analyses, and the results are summarized in Table 3. A decrease of first seizure time results in a 0.5% increase in delay of ceasing ASM before 12 months [Odds ratio (OR): 1-0.995 = 0.005]. The likelihood of ceasing ASM before 12 months decreased by 7.6 times when poly-therapy was used at the NICU discharge, while the presence of structural brain abnormalities caused a decrease of ceasing ASM by 6.3 times. Increased spike activity raised the likelihood of delaying stopping ASM before 12 months by a factor of 6.8. Also, there was a 35-fold increase in the likelihood that stopping ASM before 12 months would take longer when there was burst suppression in the EEG. The likelihood of delaying stopping ASM before 12 months was reduced by 3.4 times with a normal EEG.

Table 1: Demographic Data of all Participants

Variables	Infants with neonatal seizure n=157	Variables	Infants with neonatal seizure n=157
Gestational week (week) mean±SD (min-max)	37.3±3.6 (25-42)	Age at first seizure(hour) mean±SD (min-max)	104.1±152.4 (1-696)
Birth weight (gr) mean±SD (min-max)	2930±870 (740, 4500)	Number of seizures (per day) mean±SD	7±14 (1- 100)
Female: Male (%, %)	0.8:1 (45.2,54.8)	Duration of ASM (month) mean±SD (min-max)	6.6±4.04 (1-12)
Delivery status NSVD (n, %)	73, 46.5	Monotherapy (n, %)	110, 70.1
C/S (n, %)	84, 53.5	Polytherapy (n, %)	47, 29.9
Family history of epilepsy (n, %)	42, 26.8	Duration of follow-up (month) mean±SD	8.5±7.5 (1-24)
Etiology (n, %)		Seizure type (n, %)	
Hypoxic ischemic encephalopathy	49, 31.2	MOTOR Tonic	44, 28
Intracerebral hemorrhage& Ischemia	24, 15.3	Clonic	41, 26.1
Infection	30, 19.1	Infantile Spasm	9, 5.7
Brain structural abnormality	12, 7.6	Myoclonic	3, 1.9
Genetic	11, 7	Sequential	11, 7
Metabolic disorders	15, 9.6	Automatism	6, 3.8
Idiopathic	16, 10.2	NON-MOTOR Autonomic	29, 18.5
		Behavioral Arrest	14, 8.9
EEG (n, %)		Neuroimaging IVH/ ICH, Ischemia (n, %) Normal	23, 14.6
Focal epileptiform abnormality	73, 46.5		85, 54.1
Normal	53, 33.8		20, 12.7
Irregular background activity	5, 3.2	Periventricular leukomalacia	4, 2.5
Increased spike activity	14, 8.9	Cystic encephalomalacia	13, 8.3
Burst suppression	12, 7.6	White Matter Abnormalities	3, 1.9
		Corpus callosum hypoplasia	9, 5.7
		Not available	

ACTH, cosyntropin (tetracosactide); ASM, anti-seizure medication; C/S, cesarean section; EEG, Encephalogram; IVH, Intraventricular haemorrhage; ICH, Intracerebral haemorrhage; NSVD, Normal Spontaneous Vaginal Delivery; SD, standard deviation.

The analysis of the determinants that affect the likelihood of cease ASM is presented in the graph of ROC was summarized in Table 4. A lower likelihood of discontinuing ASM was associated with the age of the first seizure occurrence being less than 45.5 hours after birth, with a sensitivity of 63.8% and specificity of 62.5%. Thus, the chance of stopping ASM was lower when the first seizure occurred before 45.5 hours after birth. Furthermore, there was a decrease in the likelihood of discontinuing ASM in neonates when the duration of ASM usage extended beyond 6.5 months (sensitivity: 59.4%, specificity: 63.6%).

Discussion

This study characterizes the determinant factors for discontinuation of ASM in infants with seizures during the neonatal period. Stopping ASM treatment with normal EEG may be safe, but if burst suppression and increased spike

Table 2: Identification of Predictive Risk Factors For The Withdrawal of Anti-Seizure Medication (ASM)

Variable		Infants had ceased ASM before 12 months n=88	Infants still on ASM after 12 months n=69	p Value
Birth weight(gr) mean±SD		3014.3±795.1	2822.7±951.9	0.332
Gestational week(week) mean±SD		37.5±3.1	36.8±4.1	0.933
Age at first seizure(hour) mean±SD		67.9.±104.2	150.2±188.5	0.001
Number of seizures (per day) mean±SD		4.9±4.7	9.7±20.1	0.334
Duration of ASM (month) mean±SD		5.2±3.4	13.4±10.7	<0.001
Family history of epilepsy (n, %)		29, 33	13, 18.8	0.048
Etiology (n, %)				0.001
Hypoxic ischemic encephalopathy		19, 21.6	30, 43.5	0.003
Intracerebral hemorrhage& Ischemia		17, 19.3	7, 10.1	0.114
Infection		19, 21.6	11, 15.9	0.373
Brain structural abnormality		3, 3.4	9, 13	0.025
Genetic		6, 6.8	5, 7.2	0.917
Metabolic disorders		9, 10.2	6, 8.7	0.747
Idiopathic		15, 17	1, 1.4	0.001
Monotherapy (n, %)		55,62.5	55, 79.7	0.020
Polytherapy (n, %)		33, 37.5	14, 20.3	
EEG (n, %)				<0.001
Focal epileptiform abnormality		37, 42	36, 52.2	0.208
Normal		46, 52.3	7, 10.1	<0.001
Irregular background activity		-, -	5, 7.2	0.011
Increased spike activity		3, 3.4	11, 15.9	0.006
Burst suppression		2, 2.3	10, 14.5	0.004
Seizure type (n, %)				0.169
MOTOR	Tonic	28, 31.8	16, 23.2	0.234
	Clonic	19, 21.6	22, 31.9	0.146
	Infantile Spasm	3, 3.4	6, 8.7	0.159
	Myoclonic	2, 2.3	1, 1.4	0.709
	Sequential	7, 8	4, 5.8	0.600
	Automatism	3, 3.4	3, 4.3	0.761
NON-MOTOR	Autonomic	18, 20.5	11,15.9	0.471
	Behavioral Arrest	8, 9.1	6, 8.7	0.931
Monotherapy (n, %)				<0.001
Phenobarbital		24, 27.3	47, 68.1	
Levetiracetam		32, 36.4	-,-	
Phenitoin		-,-	2, 2.9	
Carbamazepine		-,-	1, 1.4	
Oxcarbazepine		-,-	4, 5.8	
Polytherapy (n, %)				
Phenobarbital+Phenitoin		14, 15.9	5, 7.2	
Phenobarbital+ Levetiracetam		17,19.3	1, 1.5	
Vigabatrin+ Phenobarbital		-	4, 5.8	
Vigabatrin+ ACTH		-	3, 4.4	
Phenobarbital+ Oxcarbazepine		1, 1.1	2, 2.9	

Neuroimaging (n, %)			0.016
IVH/ ICH, Ischemia	9, 10.2	14, 20.3	0.078
Normal	57, 64.8	28, 40.6	0.003
PVL	8, 9.1	12, 17.4	0.123
Cystic encephalomalacia	2, 2.3	2, 2.9	0.806
WM Abnormalities	8, 9.1	5, 7.2	0.678
CC hypoplasia	1, 1.1	2, 2.9	0.425
Not available	3, 3.4	6, 8.7	0.159

ACTH, cosyntropin(tetracosactide); ASM, anti-seizure medication; EEG, Encephalogram; IVH, Intraventricular haemorrhage; ICH, Intracerebral haemorrhage; PVL, Periventricular leukomalacia; WM, White Matter; CC, Corpus callosum; SD, standard deviation. Statistically significant P-values are in bold

Table 3: Logistic Regression Analysis To Determine Risk Factors For Unable To Stop Anti-Seizure Medication Before 12 Months of Age

Variables	Multivariate logistic regression analysis (Enter step1)				
	Wald statistic	P	OR	95% CI	
Age at first seizure(hours)	8.076	0.004	0.995	0.992	0.998
Aetiology as structural abnormality of brain (presence vs absence)	4.016	0.045	6.283	1.041	37.913
Poly-therapy use at the discharge	9.396	0.002	7.606	2.078	27.836
Presence of normal EEG	4.479	0.034	3.398	1.095	10.548
Presence of increased spike activity	5.239	0.022	6.824	1.318	35.340
Presence of burst suppression	11.343	0.001	34.992	4.420	277.005

Variables with P > 0.25 in the univariate analysis were excluded from multivariate analysis. Nagelkerke R-squared:0.566 (r squared>0.2), and Hosmer and Lemeshow P: 0.238,(P>0.05)was a good fit for the model. EEG, Encephalogram; OR: Odds ratio; CI: Confidence interval; ASM: Anti-seizure medication; LR: Likelihood ratio

activity are present, drug discontinuation should be gradual. Poly-therapy protocol at NICU discharge and etiology of structural brain abnormality are other red flags for rapid cessation of ASM. Younger age at the first seizure (< 45.5 hours) should be considered to increase the probability of long-term ASM usage. The most of the neonatal seizures are temporary and caused by sudden changes in metabolic levels, infections, or focal lesions in the brain (10). Hence these provoked seizures are not classified as epilepsy, long-term treatment is redundant. The main goal of continued ASM is to ensure seizures do not reoccur (12). However, recent studies have shown that the use of ASMs to treat neonatal seizures does not have an effect on the latent period or the overall likelihood of developing early onset epilepsy syndrome (15, 16). Glass and colleagues (11) suggested that it is safe to discontinue ASM after resolution of acute symptomatic seizures in neonates before hospital discharge. Acute neonatal seizures have been the primary focus of prior research on the duration of ASM use in neonates. But seizure burden can make it difficult to determine a definitive diagnosis. Early childhood epilepsies are more prevalent in areas with higher levels of social deprivation, indicating a significant social gradient. As a result, greater resources will be needed to address this issue in these regions (17). Our study has supported the utility of neuroimaging (structural abnormalities) and EEG (background activity) in guiding diagnosis in these situations.

Neonatal seizures are most commonly caused by acute neurologic disorders, including hypoxic-ischemic encephalopathy (38%), ischemic stroke (18%), and intracranial bleeding (12%) (18). Consistent with the literature, this research found that the most common etiologies of neonatal seizures are HIE (31.2%), infections (sepsis, meningitis, encephalitis) (19.1%) and intracerebral hemorrhage & ischemia (15.3%). Though most neonatal seizures are due to acute brain injury, around 15% of neonates suffer from neonatal epilepsy syndromes, which are caused by brain malformations or genetic reasons (19). In line with previous studies, 7% of our cohort had genetic

Table 4: Receiver Operating Characteristic (ROC) Analysis Results

	AUC	SE	p	95% CI		Cut-off	Sensitivity (%)	Specificity (%)
Age at first seizure (hour)	0.653	0.045	0.001	0.565	0.742	45.5	63.8	62.5
Duration of ASM (month)	0.738	0.042	<0.001	0.656	0.820	6.5	59.4	63.6

AUC: Area under the curve; CI: Confidence interval; ASM: Anti-seizure medication; SE: Standard error

etiologies and 7.6% had structural brain malformations.

The clinical diagnosis of neonatal seizures could be quite challenging due to subtle clinical motor signs or could be masked by electro-clinical uncoupling with the medications despite the presence of obvious electrographic seizure activity on EEG (4, 20, 21). Anti-seizure medicine can be initiated when EEG is unavailable by estimating the probability that clinical episodes are seizures based on diagnostic certainty levels (21). For instance, the Brighton Collaboration justifies the beginning of ASM when a motor phenomenon suspected of being an epileptogenic seizure has a focal clonic or tonic seizure characteristic (with or without EEG verification) (10). Our study found that tonic (28%) and clonic (26.1%) seizures were the most commonly observed types due to their easy detectability by observers. One unexpected finding was the extent to which we did not find a significant relationship between the duration of drug discontinuation and the seizure type of the neonates.

Tekgül et al. (22) suggested that EEG and neuroimaging play a crucial role in on determining the neurodevelopmental outcomes of seizures in term newborn infants. A neonatal EEG that is normal or mildly abnormal is associated with favorable outcomes, especially if neonatal neuroimaging is also normal. However, if the EEG is moderate/severely abnormal or if there are multifocal/diffuse cortical or primarily deep gray matter lesions, the outcome is worse. In accordance with existing literature, our findings suggest that individuals with a regular EEG pattern are prone to discontinuing the drug early, while those with structural brain abnormalities and abnormal EEG patterns are more likely to continue using it for an extended period.

Unlike neonates with early-onset epilepsy who typically require long-term ASMs, the ideal duration of ASM for infants experiencing acute symptomatic seizures is unknown (12). A recent meta-analysis strongly recommends discontinuing ASMs before discharge home, regardless of MRI or EEG results, after the resolution of acute provoked seizures in which there is an absence of evidence of neonatal-onset epilepsy (4). However, identification of the etiology in neonatal seizures can prove to be a challenging task, particularly when distinguishing early-onset epilepsy from acute provoked seizures is hindered by suboptimal resources. The aim of our study was to identify the determinant factors that encourage physicians to cease ASM in neonates.

The generalizability of these results is subject to certain limitations. Due to the small sample size, we were unable to explore the correlations between all ASMs and treatment duration separately. The retrospective design of the study limits our ability to determine the long-term outcomes of the infants. An investigator bias due to this being a single-center study is an additional uncontrolled factor. Notwithstanding the relatively limited sample, this research provides valuable insights into physicians' decision-making process when discontinuing ASM for neonatal seizures and emphasizes the importance of not delaying treatment under certain circumstances. Considerably more work will need to be done to determine specific algorithms and standards for the management of neonates' seizures and elucidate the precise duration of treatment.

In conclusion, the optimal length of ASM duration for infants experiencing acute neonatal seizures is unknown, but neonates with early onset epilepsy usually need long-term ASM. The objective of maintaining ASM is to prevent the recurrence of seizures. The purpose of the current study was to assess the determinant factors of ceasing ASM in infants with neonatal seizures. One of the more significant findings to emerge from this study is that EEG is crucial for commenting on ASM duration, and abnormal findings in the EEG should be meticulously evaluated before ceasing ASM. The subsequent major finding emphasized the importance of refraining from expeditious withdrawal of ASM in neonates presenting with seizures caused by underlying structural abnormalities of the brain. Overall, this study strengthens the idea that the discontinuation of ASM after the acute

symptomatic neonatal seizures before discharge is safe. The formulation of exact diagnostic criteria for early-onset epilepsy, coupled with the opportunity for genetic testing, will significantly strengthen the capabilities of clinicians in their detection and management of neonatal seizures. This new understanding should help to improve the prevention of the predicted unfavorable impacts of ASM on the outcome of the immature brain.

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