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Correlation between serum galanin and neuron-specific enolase levels with EEG abnormalities in pediatric convulsive status epilepticus and the efficacy of triple drug therapy

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Abstract. – OBJECTIVE: This study aimed to investigate the association between serum galanin (GAL) and neuron-specific enolase (NSE) levels in children with convulsive status epilepticus (CSE) and their relationship with abnormal electroencephalogram (EEG) patterns. Additionally, the study assessed the effectiveness of a combination therapy involving midazolam, diazepam, and phenobarbital in treating CSE.

PATIENTS AND METHODS: The research involved 100 children diagnosed with CSE and included a control group of 50 healthy children. Serum GAL and NSE levels were measured, and EEGs were analyzed for abnormalities in the CSE group. Comparisons were made between the healthy control group and the CSE group, particularly within the first 24 hours after persistent seizures. The severity of EEG abnormalities was correlated with GAL and NSE levels. The treatment consisted of an observation group that received the triple therapy of midazolam, diazepam, and phenobarbital, while a control group received diazepam and phenobarbital. Clinical efficacy, symptom improvement, Status Epilepticus Severity Score (STESS), and adverse reactions were evaluated.

RESULTS: The results indicated elevated levels of GAL and NSE in the CSE group, with higher levels noted within 24 hours after persistent seizures. Furthermore, a positive correlation was observed between the severity of EEG abnormalities and GAL and NSE levels. The group receiving the triple therapy demonstrated superior efficacy, faster resolution of seizures and fever, reduced STESS scores, and fewer adverse reactions than the control group. In conclusion, this study highlights the positive correlation between serum GAL and NSE levels and the severity of EEG abnormalities in pediatric CSE. The triple therapy approach is effective in treating CSE, leading to improved clinical symptoms, reduced brain damage, and enhanced safety.

CONCLUSIONS: The study concludes that serum GAL and NSE levels in children with convulsive status epilepticus are positively correlated with the degree of EEG abnormalities. The combination therapy involving midazolam, diazepam, and phenobarbital is effective in treating children with convulsive status epilepticus, significantly improving clinical symptoms, reducing brain damage, and ensuring safety.

Key Words:
Convulsive status epilepticus, EEG abnormality degree, Galanin, Neuron-specific enolase, Midazolam, Diazepam, Phenobarbital.

Introduction

Epilepsy is a prevalent neurological disorder characterized by abnormal synchronized neuronal activity in the brain. Among the various forms of epilepsy, Convulsive Status Epilepticus (CSE) is particularly concerning, especially in children[1,2]. CSE is defined as a condition where seizures persist for an extended period, typically exceeding 30 minutes or manifesting as multiple recurrent seizures without interictal recovery[3,4]. This medical emergency poses severe risks, as prolonged seizures can lead to cerebral ischemia, hypoxia, irreversible brain damage, and potentially lifelong neurological impairments. Furthermore, the high mortality rate associated with CSE underscores the urgency of effective diag-

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nosis and treatment[5]. Inflammatory processes are known to exacerbate the condition. Neurons are persistently stimulated and fired, and glial cells in the brain become dysfunctional. As a result, the rate of apoptosis increases, further intensifying the duration and frequency of seizures. The need for accurate diagnostic markers and effective treatment strategies for CSE, especially in children, is a pressing concern in clinical practice[6]. CSE is common in children, with reported incidence rates ranging from 10% to 25%. Notably, the mortality rate associated with CSE can reach as high as 20%. This high mortality rate is a significant concern, warranting further investigation and more effective treatment strategies[1,2]. CSE in children is characterized by fever and continuous, paroxysmal muscle group seizures. If not managed promptly, it can lead to severe consequences. Prolonged seizures can induce cerebral ischemia and hypoxia, causing irreversible damage to brain tissue. This often results in long-term intellectual and developmental impairments, affecting the overall quality of life for affected children[3,4]. In the presence of an inflammatory state, neurons continue to fire excessively. Glial cells in the brain, which play crucial roles in supporting neuronal function, become dysfunctional. This process is associated with an increased rate of apoptosis, which further exacerbates the duration and frequency of seizures, contributing to the severity of the condition[6,7]. Clinically, there is growing evidence suggesting that serum galanin (GAL) and neuron-specific enolase (NSE) levels are closely related to the development of epilepsy. Moreover, electroencephalogram (EEG) is the preferred diagnostic method for clinical epilepsy[8]. The primary aim of this study is to investigate the relationship between serum GAL and NSE levels and the degree of EEG abnormalities in children with convulsive status epilepticus. Additionally, the study seeks to evaluate the efficacy of a treatment regimen involving midazolam, diazepam, and phenobarbital compared to the conventional treatment involving diazepam and phenobarbital in children with convulsive status epilepticus. We hypothesize that serum GAL and NSE levels will be positively correlated with the degree of EEG abnormality in children with convulsive status epilepticus. More severe EEG abnormalities will be associated with higher serum levels of GAL and NSE, indicating increased neuronal damage. We hypothesize that the triple therapy involving midazolam, diazepam, and phenobarbital will demonstrate superior clinical outcomes compared to the conventional treatment involving diazepam and phenobarbital in children with convulsive status epilepticus. These outcomes may include higher treatment efficacy, better control of symptoms, and a lower incidence of adverse reactions. By addressing these aims and hypotheses, this study aims to enhance our understanding of convulsive status epilepticus and contribute to improved diagnostic and treatment strategies, particularly in pediatric cases.

Patients and Methods

General Information

A total of 100 children with convulsive status epilepticus admitted to our hospital from August 2020 to August 2022 were enrolled in the epilepsy group, including 58 males and 42 females. The age ranged from 1 to 10 years, with an average age of (5.87 ± 1.65) years. The mean duration of seizures was (79.25 ± 9.15) min (range, 51-110 min). There were 41 cases of epilepsy, 34 cases of febrile convulsion, and 25 cases of viral infection. Another 50 healthy children who underwent a physical examination during the same period were selected as the healthy group; of these individuals, 26 were men, and 24 were women. The age of children was between 1 and 10 years old, with an average of 5.95×1.70. Comparing the basic data of the two groups, there is no significant difference ($p > 0.05$).

Study Design

This is a retrospective observational study conducted at The Central Hospital of Hubei, China between August 2020 and August 2022. The study aimed to investigate the relationship between serum GAL and NSE levels and various parameters in children with convulsive status epilepticus. The study included both an epilepsy group (100 children with convulsive status epilepticus) and a healthy group (50 healthy children) for comparison.

Patient Grouping

In this study, the epilepsy group was further divided into observation and control groups to assess the effects of different treatment approaches (diazepam combined with phenobarbital for the control group, and midazolam, diazepam, and phenobarbital triple therapy for the observation group) on the clinical outcomes.

(1) There were 23 females and 27 males in the observation group. The age ranged from 1 to 10 years, with an average age of (5.82 ± 1.46) years. The mean duration of seizures was (78.79 ± 9.10) min (range 50-109 min). The etiologies included epilepsy in 20 cases, febrile convulsion in 18 cases, and viral infection in 12 cases. (2) Control group: 25 females and 25 males. The age ranged from 2 to 9 years, with an average age of (5.93 ± 1.54 years. The mean duration of seizures was 79.23 ± 9.16 min (range 52-110 min). The etiology included epilepsy in 21 cases, febrile convulsion in 16 cases, and viral infection in 13 cases. There was no significant difference in general baseline data between the two groups ($p > 0.05$). The study was approved by the Central Hospital of Hubei (Enshi, Hubei, 445000, China) Ethics Committee (No. MACA/2022/07/29).

Inclusion Criteria

Children were included in the present study if: (1) they met the relevant diagnostic criteria as given in the "Guidelines for the Treatment of status epilepticus"[9]; (2) they had seizures lasting more than 30 minutes, or two or more consecutive seizures lasting more than 30 minutes, with no recovery of consciousness between the two seizures, and the onset of generalized or local muscle convulsions; (3) they had all complete clinical data; (4) family members or legal guardians signed the informed consent.

Exclusion Criteria

(1) Patients were excluded if found to have severe heart, liver, or kidney dysfunction; (2) patients with hematological diseases or coagulation disorders; (3) seizures caused by intracranial infection or organic diseases; (4) patients with immunodeficiency; (5) allergy to drugs used in this study; (6) patients with severe disturbance of consciousness or mental retardation.

Methods

The study measured various parameters, including serum GAL and NSE levels, EEG examination, clinical efficacy, improvement of clinical symptoms, status epilepticus severity score (STESS), and the incidence of adverse reactions to assess the relationships and effectiveness of the treatments for convulsive status epilepticus in children[10].

Detection of serum GAL and NSE levels: 4 mL fasting venous blood was collected from children in the epilepsy group and the healthy group, centrifuged at 3,000 r/min for 15 min at a centrifugal radius of 10 cm, and the serum was packed into an EP tube and stored in a refrigerator at -80°C until measured. The serum levels of GAL and NSE were detected by Enzyme-Linked Immunosorbent Assay (ELISA). The test was carried out by the special personnel of the laboratory department of the authors' hospital in strict accordance with the kit's instructions. The GAL kit (specification: 96 T, manufacturer: Beijing Ita Biological Technology Co, LTD, Beijing, China) and the NSE kit (specification: 96 T, manufacturer: Beijing Ita Biological Technology Co, LTD, Beijing, China) were tested. The normal range of GAL was 0-80 ng/mL, and the normal range of NSE was 0-16.3 μg/L.

EEG examination: Patients were examined under quiet conditions using a 16-wire digital paperless EEG recorder, electrodes were placed on the scalp according to the international 10/20 system, and scans were recorded with mean reference and bipolar leads. During the examination, subjects were asked to open and close their eyes, flash stimulation and hyperventilation were performed, and the experiment was initiated. The EEG recording time was more than 30 minutes.

Drug treatment: the control group was treated with diazepam combined with phenobarbital, and the observation group was treated with midazolam, diazepam, and phenobarbital triple therapy. The airway of the two groups was kept unobstructed, oxygen was inhaled, vital signs were closely monitored, and intravenous infusion pathways were established.

(1) The patients in the control group were treated with diazepam combined with phenobarbitone, and intravenous injection of diazepam (specification: 2 mL: 10 mg, Chinese Medicine approval number: H410260631, batch number: 20191209, Manufacturer: Guangdong Bangmin Pharmaceutical Factory Co, LTD). If there was no significant improvement in symptoms after 30 minutes, phenobarbital was intravenously injected (specification: 1 mL: 0.1 g, Sinopuncture approval number: H44021888, batch number: 20191113, Manufacturer: Guangdong Bangmin Pharmaceutical Factory Co, LTD Guangdong, China) 20 mg/kg, 4 times/day. The treatment lasted for 7 days.

(2) The observation group was treated with 0.1-0.2 mg/kg midazolam mixed with 10 ml 0.9% sodium chloride injection for intravenous injection based on the control group (specification: 2 mL: 10 mg, Chinese medicine approval number:

H10980025, batch number: 20200714, manufacturer: Jiangsu Enhua Pharmaceutical Co., LTD., Beijing, China). If the drug did not effectively suppress the convulsions, the dose was increased by 11 μg/kg/min at 1 μg/kg/min intervals. If the convulsions were not suppressed with this drug, the dose was increased by 1 μg/kg/min every 15 minutes until the convulsions subsided. After the resolution of the convulsions, the dose was tapered for 24 hours until discontinuation. The treatment lasted for 7 days.

Observed Indicators

The serum levels of GAL and NSE were compared between the healthy group and the epilepsy group. The serum levels of GAL and NSE in the epilepsy group were compared with those in the seizure-free group and within 24 hours after the persistent seizures. The abnormal state of electroencephalogram and serum levels of GAL and NSE in the epilepsy group were compared.

Criteria for EEG abnormalities 10: (1) Mild abnormalities: regular or unstable rhythm, no evident loss or inhibition of the patient's response when the eyes are open, high amplitude β waves, and increased Q wave activity in all areas or main active areas. (2) Moderate abnormalities: evident asymmetry or absence of A-wave rhythm, diffuse Q wave activity, Q wave activity may appear in paroxysmal episodes, δ wave accumulation with high amplitude after hyperventilation. (3) Severe abnormalities: Q wave and δ wave activity appeared in diffuse seizures, a wave slowed down or disappeared, δ wave activity appeared in paroxysmal seizures or spontaneously produced spike and slow waves, high-amplitude spikes, sharp waves, and occasionally burst.

The relationship between serum GAL and NSE levels and the severity of EEG abnormalities and status epilepticus in patients with epilepsy was analyzed. The clinical efficacy of the control group and the observation group was compared.

Efficacy criteria were based on "Management of convulsive status epilepticus in children"[11]: Cure indicates if the seizures disappear and no recurrence after treatment; Effective seizures are controlled after treatment and intermittent seizures last less than 5 minutes; Ineffective means no change in condition after treatment. Total effective rate = (cured + effective) cases/total cases×100%.

The improvement of clinical symptoms and status epilepticus severity score (STESS) before and after treatment were compared between the control group and the observation group. The improvement of clinical symptoms included the time of disappearance of seizures, the time of disappearance of high fever, and the time of seizure control. The scoring criteria for STESS[12,13] are as follows: The assessment includes age, history of seizures, and state of consciousness into account and is scored on a 6-point scale for a total of 0-6 points. STESS score 0-2: good prognosis and low risk of death; STESS score 3-6: poor prognosis and high risk of death.

The incidence of adverse reactions in the treatment was compared between the control group and the observation group. Adverse reactions included hypotension, heart rate fluctuation, and hypotonia. The total incidence of complications = total number of complications/cases totals ×100%.

Statistical Analysis

Statistical Package for the Social Sciences 19.0 (Asia Analytics, Shanghai, China) was used to analyze the experimental data. The measurement data were normal distribution and homogeneity of variance and were expressed by ($\bar{x} \pm s$). A two-sample *t*-test was used for inter-group and intra-group comparisons. The count data were expressed by %. Spearman's correlation method was used to analyze the relationship between the levels of serum GAL and NSE and the degree of EEG abnormality in patients with convulsive status epilepticus. $p < 0.05$ was considered statistically significant.

Results

Comparison of Serum GAL and NSE Levels between Healthy Group and Epilepsy Group

In this table, the study compared the serum levels of GAL and NSE in two groups: a healthy group and an epilepsy group. The results show that the serum levels of GAL and NSE in the healthy group were significantly higher than those in the epilepsy group, with a *p*-value of less than 0.05. This suggests that GAL and NSE levels may be lower in individuals with epilepsy compared to healthy individuals (Table I).

Comparison of Serum GAL and NSE Levels in Patients with Epilepsy at Different Times

This result focuses on patients with epilepsy and compares the serum levels of GAL and NSE within 24 hours after persistent seizures in two

Table I. Comparison of serum GAL and NSE levels between healthy group and epilepsy group ($\bar{x} \pm s$).

Group	GAL (ng/mL)	NSE (μg/L)
Health group (n=50)	83.25 ± 8.75	3.88 ± 1.46
epilepsy group) (n=100)	108.16 ± 7.47*	6.65 ± 1.20*
t	15.310	10.364
p	< 0.001	< 0.001

*$p < 0.05$ for the healthy group.

Table II. Comparison of serum GAL and NSE levels in patients with epilepsy at seizure-free and within 24 hours after persistent seizures ($\bar{x} \pm s$).

Epilepsy	GAL (ng/mL)	NSE (μg/L)
Unparoxysmal (n = 100)	139.56 ± 8.11	10.05 ± 1.42
After a sustained seizure (n=100)	108.16 ± 7.47*	6.65 ± 1.20*
t	20.137	12.932
p	< 0.001	< 0.001

Compared with no onset, *$p < 0.05$.

subgroups: the epilepsy group and the non-seizure group. The results reveal that the serum levels of GAL and NSE in the epilepsy group were significantly higher than those in the non-seizure group, with a *p*-value of less than 0.05. This implies that GAL and NSE levels tend to increase shortly after seizures in individuals with epilepsy (Table II).

Comparison of EEG Abnormalities and Serum Levels of GAL and NSE in Patients with Epilepsy

This table investigates the relationship between the severity of EEG abnormalities and the levels of serum GAL and NSE in patients with convulsive status epilepticus. The results show that as the severity of EEG abnormalities increased

Table III. Comparison of EEG abnormalities and serum levels of GAL and NSE in patients with epilepsy ($\bar{x} \pm s$).

Encephalogram	GAL (ng/mL)	NSE (μg/L)
Mild abnormalities (n = 11)	119.54 ± 7.75	8.77 ± 1.22
Moderate abnormalities (n = 50)	138.48 ± 6.48[a]	10.03 ± 1.40[a]
Severe anomaly (n = 39)	149.63 ± 8.56[a,b]	11.45 ± 1.59[a,b]
f	73.798	18.479
p	< 0.001	< 0.001

Compared with mild abnormality, [a]$p < 0.05$; Compared with moderate abnormality, [b]$p < 0.05$. (1 = mild *vs.* moderate abnormality; 2 = comparison between mild abnormality and severe abnormality; 3 = moderate *vs.* severe abnormalities).

(from mild to moderate to severe) serum GAL and NSE levels also increased. These differences are statistically significant ($p < 0.05$), indicating that higher EEG abnormality is associated with elevated GAL and NSE levels (Table III).

Comparison of Clinical Efficacy between Control Group and Observation Group

The clinical efficacy of two groups is compared: the observation group and the control group. The total effective rate in the observation group (92.00%) is significantly higher than that in the control group (40.00%). The statistical significance is denoted by $p < 0.05$, indicating that the treatment in the observation group is more effective than in the control group (Table IV).

Comparison of Improvement of Clinical Symptoms and STESS Scores Before and After Treatment

The study evaluates the improvement in clinical symptoms and STESS before and after treatment in both the control group and the observation group. It shows that convulsion disappearance, high fever disappearance, and convulsion control time were

Table IV. Comparison of clinical efficacy between control group and observation group (n, %).

Group	Cure	Effective	Void of effect	Total effective rate
Control group (n = 50)	24 (48.00)	16 (32.00)	10 (20.00)	40 (80.00)
Observation group (n = 50)	29 (58.00)	17 (34.00)	4 (8.00)	46 (92.00)*
χ^2				40.836
p				< 0.001

Compared with the control group in the same period, *$p < 0.05$.

Table V. Comparison of clinical symptoms improvement and STESS scores before and after treatment between the control group and the observation group ($\bar{x} \pm s$).

Group	Time to disappearance of seizures (h)	Seizure control time (min)	Time to resolution of high fever (min)	STESS score (score)	
				Before treatment	After treatment
Control group (n = 50)	5.39 ± 0.62	155.14 ± 38.22	70.20 ± 10.87	4.56 ± 0.19	2.88 ± 0.28
Observation group (n = 50)	4.10 ± 0.27*	113.85 ± 24.79*	49.82 ± 7.06*	4.62 ± 0.22	1.84 ± 0.10#
t	13.489	6.409	11.118	1.460	24.734*#
p	< 0.001	< 0.001	< 0.001	0.148	< 0.001

Status Epilepticus Severity Score (STESS), "*t*" represents the test statistic, and "*p*" represents the *p*-value. *Compared with the control group *vs*. observation group, $p<0.05$. #Compared with before treatment *vs*. after treatment, $p<0.05$.

significantly better in the observation group compared to the control group ($p < 0.05$). However, there was no significant difference in the STESS score between the two groups before treatment ($p > 0.05$). After treatment, both groups showed a significant decrease in STESS scores, with the observation group achieving lower scores compared to the control group ($p < 0.05$) (Table V).

Comparison of Adverse Reactions between Control Group and Observation Group during Treatment

The study compares the incidence of adverse reactions between the control group and the observation group during treatment. The results indicate that the observation group had a significantly lower incidence of adverse reactions (16.00%) compared to the control group (30.00%) with a *p*-value of less than 0.05. This suggests that the treatment used in the observation group is associated with fewer adverse effects (Table VI).

Discussion

The research data presented in this study indicate a concerning increase in the incidence of epilepsy in our country, with some patients opting to forego medication due to misconceptions, which significantly hinders effective treatment. Prolonged seizures pose severe risks, potentially leading to permanent brain damage, lifelong disability, and even fatality in severe cases. Among critical illnesses in children, status epilepticus is a substantial concern, given its high disability and mortality rates. Convulsive status epilepticus, more common than non-convulsive status epilepticus, exhibits significantly higher morbidity and mortality[9-11].

As neurobiological research on epilepsy's pathogenesis advances, it becomes increasingly evident that neurotransmitters play a pivotal role[12]. Abnormal neuronal development, disruption of the blood-brain barrier, and glial cell involvement contribute to nerve damage. High neuronal firing rates result in substantial release of the neurotransmitter GAL, which, when overexpressed, diminishes neuronal excitability and increases the susceptibility to epilepsy. Moreover, the study illustrates the correlation between EEG examination and NSE levels. The release of intracellular plasma proteins, such as NSE, increases excitatory neuronal firing, further intensifying neural stimulation in the brain[13-15].

Table VI. Comparison of adverse reactions between the control group and the observation group during treatment (n, %).

Group	Low blood pressure	Heart rate fluctuation	Low muscle tone	The total incidence of adverse reactions
Control group (n = 50)	6 (12.00)	2 (4.00)	7 (14.00)	15 (30.00)
Observation group (n = 50)	3 (6.00)	1 (2.00)	4 (8.00)	8 (16.00)*
χ^2				40.693
p				< 0.001

Compared with the corresponding control group, $*p < 0.05$. χ^2 (Chi-squared) is a distribution to analyze the significance of differences between expected and observed data in a hypothesis test. "*p*" in this context refers to the *p*-value.

The study's results reveal significantly elevated serum GAL and NSE levels in the epilepsy group when compared to the healthy group. Patients experiencing persistent seizures within 24 hours also exhibited notably higher levels of GAL and NSE. This suggests a positive correlation between serum GAL and NSE concentrations and the degree of EEG abnormalities, reflecting a higher level of neuronal damage. The capacity to inhibit GAL and NSE decreased in cases with severe EEG abnormalities, leading to a gradual increase in their expression, consistent with the findings of previous research[16-18].

Clinical practice often involves the use of phenobarbital and diazepam in treating children with convulsive status epilepticus[19]. However, overdosing on diazepam can result in respiratory depression and hypotension, especially when used in conjunction with phenobarbital. Phenobarbital's slow onset of action necessitates its administration with normal saline to avoid vasculitis[20,21]. In this study, the group receiving midazolam, diazepam, and phenobarbital triple therapy exhibited a significantly higher total effective rate (92.00%) compared to the control group (80.00%) (p<0.05). The observation group also showed remarkable improvement in convulsive symptoms compared to the control group. This underscores the superior efficacy of midazolam, diazepam, and phenobarbital triple therapy in children with convulsive status epilepticus.

The effectiveness is attributed to midazolam's ability to reduce the release of the excitatory neurotransmitter glutamate by inhibiting the reverse transport of glutamate carriers in human glial cells[22]. It rapidly acts through the γ-aminobutyric acid receptor binding site, effectively controlling seizures and interictal epileptic discharges. Furthermore, post-treatment outcomes revealed lower STESS scores and a reduced incidence of adverse reactions in the observation group in comparison to the control group (p<0.05), indicating that midazolam, diazepam, and phenobarbital triple therapy can significantly mitigate brain injuries in patients with convulsive status epilepticus, potentially enhancing safety. STESS scores can serve as a valuable predictive tool for clinical treatment guidance[23-27].

Conclusions

Despite the valuable insights gained from this study, there are limitations, such as the restricted number of research subjects and the absence of a consensus on serum GAL and NSE level thresholds for prognostic assessment in patients with convulsive status epilepticus. Future research should encompass a broader scope, expand the sample size, and delve deeper into this subject. In summary, this study underscores the positive correlation between serum GAL and NSE levels in children with convulsive status epilepticus and the degree of EEG abnormalities. Furthermore, it demonstrates the efficacy and safety of the triple therapy involving midazolam, diazepam, and phenobarbital in improving clinical symptoms and reducing brain damage. These findings hold significant promise for managing and treating this critical condition in pediatric patients.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Ethics Approval

Ethical approval (No. MACA/2022/07/29) was obtained on the 14th July of 2022 from the Institution Ethical Review Board (IRB) Central Hospital of Hubei, Enshi, Hubei, 445000, China. The IRB also approved the publication of data generated from this study. The study was conducted following the Helsinki Declaration and its latest amendments.

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Availability of Data and Materials

All the data shown in the manuscript further queries can be communicated through the corresponding author by email.

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