Cefepime-induced encephalopathy: Neural mass modeling of triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC)

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Aim: Cefepime, a fourth-generation cephalosporin, acts as a GABA\textsubscript{A} receptor antagonist. Cefepime-induced encephalopathy (CIE) is frequently overlooked. We aimed to clarify the clinical features, characteristic electroencephalography (EEG), and mechanisms of CIE to aid in its early recognition.

Methods: CIE cases documented by a single-center consultation–liaison team between April 2015 and March 2017 were retrospectively reviewed. For further investigation, neural mass modeling was performed in silico.

Results: Three patients with CIE refused medication/examination and showed overt pain, pallialia, and much greater deterioration of eye and verbal response than the motor response, which was possibly related to GABAergic dysfunction. Triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC) were identified on the EEG of all three cases. The simulation reproduced the characteristic feature of 2-3 Hz Tri-HNC and recovery course on EEG, and a possible involvement of individual differences in pharmacological intervention. It also suggested that auto-inhibition (synaptic inputs from interneuron to interneuron) dysregulation contributed to generating Tri-HNC in CIE.

Conclusion: As CIE is iatrogenic and continues unless cefepime is stopped, early recognition is crucial. Physicians should be vigilant about altered mental status, pain, and verbal changes in patients taking cefepime. Tri-HNC on EEG can expedite the diagnosis of CIE, and the association between Tri-HNC and CIE suggests that an excitatory and inhibitory imbalance due to the dysfunction of GABAergic interneurons is the underlying mechanism. This modeling may offer a new method of investigating disorders related to GABAergic dysfunction.

Keywords: computer simulation, electroencephalography, encephalopathy, GABAergic neurons, non-convulsive status epilepticus.

Methods

Clinical data collection and ethical considerations

Three patients with CIE were referred to the consultation–liaison (C-L) team between April 2015 and March 2017 at Tokyo Metropolitan Tama Medical Center, a 789-bed tertiary care teaching hospital in Tokyo, Japan. The C-L service, which is available around-the-clock, receives approximately 850 patients annually. EEG were recorded for all three patients. Twenty-one electrodes (13 out of 21 for a simplified recording) were placed on the scalp in accordance with the International 10–20 system. The time constant and the high-cut filter were set to 0.3 s and 60 Hz, respectively. We obtained written informed consent from Patients 1 and 2, and the study was approved by the institutional review board at Tokyo Metropolitan Tama Medical Center with a waiver of informed consent from Patient 3 (due to death).

Neural mass modeling

In the simulation, we used a spatially homogeneous version of neural mass modeling, which is basically a mean field model of the cortex.\textsuperscript{5,6} Figure 1a,b present an overview of the model. The model...
describes the dynamics of the average membrane potentials of a cortical macrocolumn comprised of excitatory (pyramidal) neurons and GABAergic inhibitory (inter-)neurons. In short, both excitatory and inhibitory neurons receive input via intracortical synaptic projections (Ex->Ex, Ex->Inh, Inh->Ex and Inh->Inh) as well as nonspecific excitatory input from regions not explicitly incorporated into the model, such as the thalamus \( p_{\pm} \sigma_{p_{\pm}} \). \( N_{kx} \) denotes the number of synaptic inputs from \( k \) to \( x \). The indices \( e \) and \( i \) refer to the excitatory and inhibitory neurons, respectively. Using the values of \( N_{kx} \), the model generates the mean voltage of the excitatory and inhibitory neurons. (c) The mean voltage of the excitatory neuron \( (N_{ex} = 3000, N_{ix} = 380) \). (d) To illustrate the simulated scalp electroencephalography (EEG), the plus and minus ends were simply reversed and arbitrary units were used for the \( y \)-axis. (e) Using normalized EEG, (f) negative/positive ratio, complex frequency, and complex duration were calculated. (g) The power of the waves and (h) spectrogram are also presented.

**Model parameters and equations**

The indices \( e \) and \( i \) used below refer to the excitatory and inhibitory neurons, respectively. The membrane potentials are denoted by \( V_k(t) \) for \( k = e, i \). Their dynamics are governed by the following set of differential equations:

\[
\tau_e \frac{dV_e}{dt} = I_{rest}^{e} - V_e(t) + \Psi_{AMPA}^{e} I_{ee}(t) + \Psi_{GABA}^{e} I_{ei}(t) + \Psi_{AMPA}^{e} I_{ne}(t),
\]

\[
\tau_i \frac{dV_i}{dt} = I_{rest}^{i} - V_i(t) + \Psi_{AMPA}^{i} I_{ei}(t) + \Psi_{GABA}^{i} I_{ii}(t) + \Psi_{AMPA}^{i} I_{ni}(t),
\]

where \( \tau_k \) and \( I_{rest}^{k} \) denote the membrane time-constants and resting-potentials, respectively, and \( I_{nk} \) is proportional to the current flowing into population \( x \) due to the activity of population \( k \). The currents \( I_{ex} \) and \( I_{ni} \) model the afferent, non-specific input to the cortical column, and are modeled as uncorrelated white-noise processes with the mean values \( p_{ni} \) and \( p_{ex} \) and the standard deviations \( \sigma_{p_{ni}} \) and \( \sigma_{p_{ex}} \), respectively. The currents \( I_{nk} \) are given by

\[
I_{nk}(t) = h_{AMPA/GABA} \otimes N_{nk} S_k(V_k(t)),
\]

where \( h_{AMPA/GABA} \) is the half-activation function of AMPA and GABA, \( N_{nk} \) is the number of synaptic inputs from \( k \) to \( x \), and \( S_k(V_k(t)) \) is the synaptic input function of population \( k \).
where \( h_{\text{AMPA/GABA}}(\tau) = \text{th}_{\text{AMPA/GABA}}(\text{AMPA/GABA}) \exp(1 - \gamma_{\text{AMPA/GABA}}) \) is the response function of AMPA/GABAergic receptors located on the dendrites of neurons within population \( k \). \( N_{kx} \) denotes the number of synaptic inputs from \( k \) to \( x \), which is a variable in this study. The function \( S_k \) relates the membrane potential of population \( k \) to its firing-rate, and is given by

\[
S_k(V_k) = \frac{Q_k^{\text{max}}}{1 + \exp\left(\frac{-\sqrt{2}(V_k(t) - V_k^{\text{rest}})}{\sigma_k}\right)}
\]

The variables \( Q_k^{\text{max}} \) are dimensionless and model the dependence of AMPA/GABAergic synaptic conductance on the membrane potential of the post-synaptic neural population \( k \). They are given by

\[
Q_k^{\text{max}} = \frac{E_{\text{AMPA/GABA}} - V_k(t)}{E_{\text{AMPA/GABA}} - V_k^{\text{rest}}}
\]

The baseline values for all model parameters were modified from previous reports\(^8\) and are listed in Table 1. For further details, see Tjepkema-Cloostermans et al.\(^6\).

**Illustrating EEG, in silico analysis, and statistics**

With the values of \( N_{kx} \), the model generated the mean voltage of the excitatory and inhibitory neurons. To simulate the scalp EEG, the plus and minus ends were simply reversed, and arbitrary units were used for the \( y \)-axis (Fig. 1c,d).

One representative recording of real or simulated EEG was normalized to its amplitude (Fig. 1e). We defined the negative/positive ratio as the amplitude ratio of negative component over positive component of each GPD. We also defined the complex frequency and the complex duration as the number of GPD shown per second and the duration of each GPD, respectively, based on peak-to-peak interval times using semi-automatic peak detection (Fig. 1f). We characterized spectral components based on fast Fourier transform (FFT). In detail, we computed the power spectrum of the whole waveform, to visualize overall characteristics (Fig. 1g), and spectrogram using half-overlapping 0.4-s time windows with a hamming window to visualize temporal variation (Fig. 1b) on MATLAB (R2018a, MathWorks, Inc., Natick, MA, USA), with a signal processing toolbox.

**Neural mass modeling**

To examine the underlying mechanism, we performed a simulation using neural mass modeling.

**Simulation of Tri-HNC and the recovery course in CIE**

We first used the same number for \( N_a \) and \( N_e \) (represented as \( N_{a/e} \)) in accordance with the original Liley model.\(^5\) To simulate cefepime-induced neurotoxicity as GABA_\(A\) receptor antagonism, \( N_{a/e} \) was decreased from 500 (100% input). As expected, \( N_{a/e} = 380 \) (76% input) partly explained the characteristic feature of Tri-HNC (Fig. 3a) while the FFT indicated the dominant frequency to be 6–7 Hz (Fig. 3b). Figure 3c shows a spectrogram corresponding to Figure 3a.

To assess the recovery course, \( N_{a/e} \) was changed from 380 in a stepwise fashion to 500. Figure 3d shows the simulated EEG at \( N_{a/e} = 380 \) (100% input). The power for each frequency (from left to right) is illustrated in Figure 3e. The dominant background activity changed from 7 Hz (\( N_{a/e} = 380 \), 76% input) to 12 Hz (\( N_{a/e} = 500 \), 100% input). The spectrograms near the phase-transition point (Fig. 3f) qualitatively reproduced the clinical recovery course (Fig. 2e).

**Simulation of pharmacological intervention**

Benzodiazepines, such as clonazepam and diazepam, are frequently used for alleviating CIE; however, their effectiveness has not been proven and may vary in individual cases.\(^9\) To investigate the effect of pharmacological intervention, we fixed \( N_{a/e} \) at 380 as a constant and moved \( N_{a/e} (= N_{e/e} = N_{a/a}) \) simultaneously from 1500 to 3000, since some interneurons are insensitive to benzodiazepines.\(^14,15\) At \( N_{a/e} = 1500 \) or 1800 (50% or 60% input, respectively), the simulated EEG showed a low voltage pattern (Fig. 4a,b). Although they showed alpha-band oscillations at \( N_{a/e} = 2100, 2400, \) and 2700 (70%, 80%, and 90% input in Fig. 4c–e, respectively), strikingly, they became unstable again at \( N_{a/e} = 3000 \) (100% input, Fig. 4f), suggesting that pharmacological intervention had transient effects and that the permanent recovery of \( N_{a/e} \) played a critical role in stability.

**Table 1. Model parameters, their symbols, and baseline values**

| Parameter                  | Symbol      | Baseline value |
|----------------------------|-------------|----------------|
| Maximum spike-rate         | \( Q_k^{\text{max}} \) | 500 s\(^{-1}\) |
| Spike-threshold            | \( V_k^{\text{rest}} \) | -60 mV         |
| SD of spike-threshold      | \( \sigma_k \) | 5 mV           |
| Synaptic efficacy          | \( H_{\text{GABA}}/H_{\text{AMPA}} \) | 0.71 mV        |
| Reversal potential         | \( E_{\text{GABA}}, E_{\text{AMPA}} \) | -90, 40 mV     |
| Number of synaptic inputs  | \( N_{kx}, N_{o/e}, N_{i/e}, N_{ii} \) | 3000, 3000, 500, |
| from k to x                |             | 500 (variable) |
| Membrane time-constant     | \( \tau_e, \tau_i \) | 0.094, 0.042 s |
| Resting potential          | \( V_k^{\text{rest}} \) | -70 mV         |
| Synaptic rate-constant     | \( V_{\text{GABA}}, V_{\text{AMPA}} \) | 65, 300 s\(^{-1}\) |
| Non-specific firing rate   | \( V_{\text{Pe}}, V_{\text{Pi}} \) | 3460, 5070 s\(^{-1}\) |
| SD of non-specific fluctuation | \( \sigma_{\text{Pe}}, \sigma_{\text{Pi}} \) | 1000, 150 s\(^{-1}\) |

The indices \( k \) and \( x \) refer to neural populations of type \( k \) and \( x \) for e (excitatory-), and i (inhibitory-) neurons.
This simulation was consistent with clinical observations and led us to form the hypothesis that the underlying mechanism involved the induction of low-voltage EEG activity in the CIE patient by high-dose benzodiazepine while low-dose (or an appropriate concentration of) benzodiazepine transiently improved awareness without maintaining full-recovery until sufficient cefepime clearance.

Table 2. Summary of three cases of cefepime-induced encephalopathy

| Age (years) | Sex  | Weight (kg) | eGFR Adjusted for renal function | Indication | Clinical findings | Latency (days) | Intervention | Days to improvement |
|-------------|------|-------------|----------------------------------|------------|-------------------|---------------|--------------|------------------|
| 64          | Female | 52.7        | 21 (on dialysis) No | Infectious endocarditis | AMS (E2V3M4), pain, palilalia, refusal of medication | 4 | Observation | 4 |
| 44          | Male  | 40.0        | No                     | Pneumonia   | AMS (E1V2M4), palilalia, refusal of examination | 5 | Observation | 4 |
| 94          | Female | 38.3        | Yes                   | Cholangitis, cellulitis | AMS (E1V2M4), pain, palilalia, refusal of medication | 4 | DZP, PHT | 4 |

AMS, altered mental status; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); DZP, diazepam 5 mg; PHT, phenytoin 250 mg.

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Excitatory and inhibitory imbalance explains the characteristic features seen on the EEG

We hypothesized that excitatory and inhibitory (E/I) imbalance was essential to explaining the features seen on the EEG. To determine which parameter was chiefly responsible for these characteristic features, we conducted stepwise parameter studies in silico.

First, we set $N_{ee}$ at 500 (100% input, constant) and experimentally changed $N_{ex}$ and $N_{ei}$ individually from 1200 to 6000 (40% to 200% input; Fig. 5a). This simulation suggested that alpha-band oscillation was robust in the condition that both $N_{ee}$ and $N_{ei}$ were under 100% input and that $N_{ee}$ basically provided the dominant frequency. It also suggested that $N_{ee}$ and $N_{ei}$ balance was a key factor of

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**Fig. 3** Simulation of triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC) and recovery course on electroencephalography (EEG). (a) Simulated EEG explains the characteristic feature of 2–3 Hz Tri-HNC (on $N_{ee} = 380$, 76% input), while (b) fast Fourier transform indicates that the dominant frequency was 6–7 Hz. (c) A spectrogram corresponding to (a). (d) The simulated EEG at $N_{ee} = 500$ (100% input). (e) Illustration of the power of each frequency component (from left to right: $N_{ee} = 380$, 390, 400, 420, 440, 460, and 500). The dominant background activity changed from 7 Hz ($N_{ee} = 380$, 76% input) to 12 Hz ($N_{ee} = 500$, 100% input). (f) The spectrograms near the phase-transition point ($N_{ee} = 380$, 381, 382, 390) qualitatively reproduced the clinical recovery course.

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**Fig. 4** Simulation of pharmacological intervention. (a,b) With $N_{ee} = 380$ as a constant, the simulated electroencephalography (EEG) showed a low-voltage pattern at $N_{ex} = 1500$ or 1800 (50% and 60% input, respectively), while (c–e) they showed alpha-band oscillations at $N_{ex} = 2100$, 2400, and 2700 (70%, 80%, and 90% input, respectively). (f) Notably, the EEG pattern became unstable again at $N_{ex} = 3000$ (100% input). These findings indicate individual pharmacological differences.
phase-transition, as previously reported.6–7 As expected, the Tri-HNC pattern can be generated at $N_{ee} = 4650$ and $N_{ii} = 5850$ (Fig. 6a), which indicated that increased E/I was essential to generate the Tri-HNC.

Cefepime theoretically antagonizes GABAergic inhibitory inputs. To determine whether $N_e$ or $N_i$ contributed more to generating GPD, we set $N_{ee} = 3000$ (100% input, constant) and changed $N_{ee}$ and $N_{ii}$ individually from 280 to 500 (56% to 100% input, Fig. 5b). This simulation suggested that $N_{ee}$ provided the dominant frequency and that $N_{ee}$ and $N_{ii}$ balance was another key factor of phase-transition, indicating that only $N_{ee}$ or $N_{ii}$ was not enough to generate GPD. Moreover, the 2–3 Hz Tri-HNC pattern was most closely reproduced at $N_{ee} = 350$ and $N_{ii} = 292$ (Fig. 6b).

To investigate another possibility that inputs to interneuron is the underlying mechanism, we set $N_{ee} = 3000$ (100% input, constant) and $N_{ee}$ and $N_{ii}$ stepwise study under $N_{ee}$ constant (data not shown). These findings demonstrated that only one parameter was insufficient to explain the GPD and that alpha-band oscillation was robust enough to overcome the external disturbance.

We also examined a possible application of neural mass modeling. With appropriate parameters, neural mass modeling generated characteristic features, such as Tri-HNC at another frequency (Fig. 6c) and spindle (Fig. 6d). These simulations suggested that E/I balance accounted for some of the characteristic features seen on the EEG.

Finally, we quantitatively compared the negative/positive ratio, complex frequencies, and complex durations of real and simulated EEG. Negative/positive ratios (Fig. 6e) did not differ statistically, whereas the complex frequencies (Fig. 6f) and the complex durations (Fig. 6g) differed statistically. The findings were based on a small number of cases and await validation by further studies.

**Discussion**

**Clinical presentation**

We noticed that 2–3 Hz GPD with a high negative component (above baseline) seemed to characterize cefepime-induced encephalopathy7–12,16–18 in contrast to the triphasic waves induced by other illnesses, such as hepatic encephalitis10 or Creutzfeld–Jakob disease.19 Moreover, the triphasic morphology with negative polarity in the dominant phase was perceived as differing from the ‘typical’ triphasic wave by clinicians (odds ratio: 0.09, 0.02–0.22),20 suggesting that the clinicians differentiated the Tri-HNC from ‘typical’ triphasic wave; however, only a few studies have focused on this characteristic feature.10,21

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**Fig. 5** Dominant frequencies and phase-transition experimentally simulated using each excitatory and inhibitory parameter. (a) $N_e$ from 1200 to 6000 (40% to 200% input) and $N_{ee}$ from 1800 to 4950 (60% to 165% input) under $N_{ee}$ constant (500, 100% input), suggesting that $N_{ee}$ provided the dominant frequency and that $N_{ee}$ and $N_{ii}$ balance was a key factor of phase-transition. (b) $N_i$ from 340 to 500 (68% to 100% input) and $N_{ee}$ from 290 to 500 (58% to 100% input) under $N_{ee}$ constant (3000, 100% input), suggesting that $N_{ee}$ provided the dominant frequency and that $N_{ee}$ and $N_{ii}$ balance was another key factor of phase-transition. (c) $N_{ee}$ from 1800 to 6000 (60% to 200% input) and $N_i$ from 430 to 500 (86% to 100% input) under $N_{ee}$ and $N_{ii}$ constant (100% input), indicating that $N_{ee}$ and $N_{ii}$ were insufficient to explain the generalized periodic discharge generation, and that alpha-band oscillation was robust enough to overcome the external disturbance. Low Vol., low voltage EEG.

*Phase-transition point.
Fig. 6 Simulation of other characteristic features and statistics. (a,b) A unique 2–3 Hz triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC) pattern similar to that seen in cefepime-induced encephalopathy was reproduced with certain parameters. (a) Ne = 4650, Nei = 5850, and Nix = 500. (b) Nex = 3000, Nie = 350, and Ni = 292. (c) Tri-HNC with another frequency (Ne = 4500, Nei = 5100, Nix = 500) and (d) spindle (Nex = 2700, Nei = 4500, Ni = 500) was also generated. (e) The negative/positive ratios ($P = 0.10$) did not differ statistically between the clinical cases and simulations, whereas (f) complex frequencies and (g) complex durations differed statistically ($P < 0.05$). Error bars indicate SD.
We identified Tri-HNC in all three C-L cases of CIE with chronic kidney disease (Fig. 2 and Table 2). Latency and days to improvement were almost the same as those previously reported, and other diseases causing altered mental status were carefully excluded in all the cases. All the patients showed a similar, characteristic clinical course (Table 2), including refusal of medication/examination, complaint of overt pain and palilalia, and much greater deterioration of eye and verbal response than the motor response. Previous reports showed that patients with CIE presented altered mental status more often than seizures or psychotic symptoms. We hypothesized that these different types of triphasic waves observed in hepatic encephalopathy, which suggested that some metabolic encephalopathies might not be approximated by the simplified mean field model of synaptic networks. Nonetheless, computational modeling may contribute to clarifying its pathophysiology and offer a new method for investigating disorders related to GABAergic dysfunction.

Neural mass modeling and the relevance of Tri-HNC detection

Our neural mass modeling reproduced the Tri-HNC and a characteristic feature seen on EEG in the course of recovery (Fig. 3) and suggested a potential mechanism for individual differences in patients’ responses to pharmacological interventions (Fig. 4). In silico analysis revealed that generating GPD was a circuit-level phenomenon and offered some hints regarding the relation between alpha-band oscillation and awareness (Fig. 5). Together with the biological insight, it also suggested that the number of synaptic inputs from interneuron to interneuron (NII, auto-inhibition) dysregulation contributed to generating Tri-HNC in CIE, although auto-inhibition dysregulation alone cannot explain the whole phenomena.

Based on the simulation of pharmacological intervention (Fig. 5), low-dose (or an appropriate concentration of) benzodiazepine can transiently improve awareness; however, sufficient cefepime clearance was suggested to be a requirement for full-recovery. Comparison with a large clinical information dataset is necessary for clarifying whether further pharmacological treatment has long-term benefit and/or side-effect. A previous case report showed that flumazenil, a GABA_A receptor antagonist, improved the triphasic waves caused by hepatic encephalopathy. We hypothesized that these different types of triphasic wave reflected essentially different activities of the brain. Although our neural mass modeling cannot provide a hypothesis as to which subtype of interneuron, such as PV, SST, or 5HT3aR, plays a key role, it emphasized the importance of the auto-inhibitory system associated with interneuron microcircuits.

Qualitatively and quantitatively, the Tri-HNC had a blunt ascent and descent with a high negative component, relatively long complex frequencies (Fig. 6e–g). Of note, we succeeded in simulating the most prominent feature, high negative component, quantitatively (Fig. 6e). The psychological clinical presentations (verbal changes, response to stimuli, and fluctuating attention) and the lack of a need for additional interventions showed that Tri-HNC differed from epileptic discharges and may require a new designation although the matter remains controversial.

To explore other possible applications of neural mass modeling, we simulated the EEG of other disorders related to the dysfunction of GABAergic interneurons. We were able to generate a 0.5–1 Hz Tri-HNC similar to that seen in some patients with glutamic acid decarboxylase antibody-associated encephalitis, who showed 0.3–0.5 Hz Tri-HNC (Fig. 6c). It is possible, at any rate, that Tri-HNC is common to various cases of GABAergic interneuron instability.

Limitations

We are aware of several limitations to this study. First, not all patients referred to the C-L team for consultation underwent an EEG examination. Although all three patients presented Tri-HNC, it is possible that other patients with CIE were overlooked as often happens in cases of delirium. Second, the number of cases was too small to draw any firm conclusions about the clinical course. Further, comprehensive, prospective studies are needed for clinical investigation.

Next, neural mass modeling was aimed for an approximation of spatially and temporally homogenous EEG. In the model, the interactions between excitatory and inhibitory neurons are averaged over the whole brain and only one excitatory neuron and one inhibitory neuron with their interactions represent the networks. Relatively complicated concepts, such as the dipole moment or source and sink, are not incorporated into the model; however, Tri-HNC may be one of the best-matched patterns in this simplified model given its spatially and temporally homogenous pattern in the real EEG. A more sophisticated model could reproduce the ‘typical’ triphasic wave, while our simplified model is just enough to reproduce Tri-HNC.

This study identified a connection between the features of real EEG and neural mass-modeling-simulated EEG, suggesting that E/I imbalance due to the dysfunction of GABAergic interneurons was the underlying mechanism of CIE (Fig. S1). As theoretical molecular mechanisms remain speculative at best, further biological experiments are needed to verify our hypothesis.

Conclusion

As CIE is iatrogenic and potentially self-limiting only when cefepime is stopped, early recognition of the symptoms is crucial. In addition to the US Food and Drug Administration recommendation to be aware of the risk of seizures and to recognize the need for dose adjustments when using cefepime, physicians also need to be more vigilant in regards to altered mental status, pain, and verbal changes in patients taking cefepime.

Neural mass modeling reproduced Tri-HNC, a characteristic feature of EEG in patients with CIE. Together with the clinical presentations, Tri-HNC can expedite the diagnosis of CIE. The association between CIE and Tri-HNC suggested that E/I imbalance due to the dysfunction of GABAergic interneurons is the underlying mechanism of CIE. This modeling may offer a new method for investigating disorders related to GABAergic dysfunction.

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Disclosure statement

The authors have no conflicts of interest to disclose.

Author contributions

H.T. conceived the study. H.T., Y.H., and N.Y. collected the data. The authors have no conflicts of interest to disclose.
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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1. Graphical abstract.