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Characteristic EEG Waveform, Tri-HNC, in Cefepime-induced Encephalopathy Due to Excitatory/inhibitory Imbalance

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Abstract

Cefepime, a fourth-generation cephalosporin with a beta-lactam ring, acts as a $GABA_A$ receptor antagonist. Cefepime-induced encephalopathy (CIE) is frequently overlooked, though a study estimated that 15% of patients treated with cefepime in the intensive care unit suffered CIE.

We noticed that patients with CIE experienced similar clinical manifestations and characteristic electroencephalography (EEG) waveforms. We aimed to reproduce these characteristic EEG waveforms and investigate the pathogenesis of CIE via computer simulation.

Three patients with CIE were retrospectively documented by a single-center

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consultation-liaison team during a two-year study period. In all the cases, the patients refused medication/examination and showed signs of overt pain, palilalia, and a much greater deterioration in eye and verbal responses than in their motor responses. These symptoms might have been misdiagnosed as a psychogenic condition; however, together with the *in silico* analyses, we suspected that the clinical manifestations were probably related to GABAergic dysfunction. To define the characteristic EEG waveforms presented by all three patients, we coined the term, "triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC, pronounced, *Try-high-neck*)".

Computer simulation using neural mass modeling (basically mean-field model) reproduced the characteristic features of Tri-HNC, the recovery course on EEG, and the individual differences in pharmacological intervention. The simulation also suggested that auto-inhibition (synaptic inputs from interneuron to interneuron) dysregulation contributed to the generation of Tri-HNC. We believe that there is a common pathophysiologic basis of excitatory/inhibitory imbalance due to GABAergic dysfunction and that Tri-HNC can be its experimental phenotype.

Given the rapid progress of basic neuroscience, enabling psychiatrists to make clinical observations, particularly with respect to psychopathology and pharmacology, and to extract homogeneous subgroups from heterogeneous patients may yield useful insights; moreover, it may promote effective patient care.

Keywords: cefepime-induced encephalopathy (CIE), GABAergic neurons, computational psychiatry, computer simulation, translational research

Introduction.

It is often difficult to accurately identify the primary cause of altered consciousness. Antimicrobial agents can cause delirium, but these possibilities are largely overlooked. Cefepime, a fourth-generation cephalosporin with a beta-lactam ring, acts as a $GABA_A$ receptor antagonist[7] and has been reported to cause cefepime-induced encephalopathy (CIE) in 15% of patients treated by cefepime in the ICU for more than 3 days[3].

It is known that the symptoms of encephalopathy vary depending on the type of antimicrobial agent (Fig. 1).[1)9)] In

CIE, altered consciousness and abnormal electroencephalogram are observed in almost all cases.[6] However, there have been no specific reports on psychiatric symptoms.

To define the characteristic EEG waveforms presented by all three patients we studied, we coined the term, "triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC, pronounced, Try-high-neck)". The characteristic morphology of the EEG was reproduced by computer simulation, and it was suggested that a disruption of the excitatory-inhibitory balance (E/I balance) was involved in the underlying mechanism.

Here we briefly introduce our study[8] as an example of a new concept proposed by computational psychiatry based on precise clinical observation of a condition with a clear pharmacological causal relationship.

I. Methods and results of the study

We retrospectively reviewed the clinical course of three patients diagnosed with CIE who were consulted to the neuropsychiatry liaison team of the Tokyo Metropolitan Tama Medical Center between April 2015 and March 2017. Based on the characteristic morphology of the EEG waveform, we suspected that the neural activity during CIE could be approximated as a spatiotemporally homogenous neuronal populations. Therefore, we performed computer simulations using neural mass modeling (one of the mean-field models)[5][10]. Informed consent was obtained from each patient and the study was approved by the ethics committee, and the study was conducted in consideration of privacy protection.

1. Clinical course of cefepime-induced encephalopathy

Cefepime is an essential broad-spectrum antimicrobial agent for empiric therapy of febrile neutropenia (FN) and healthcare-associated infections because of its bactericidal activity against *Pseudomonas aeruginosa* and multidrug-resistant Gram-negative Enterobacteriaceae[9].

As in the previous reports, our all three cases of CIE were associated with impaired renal function. Since almost all beta-lactam antimicrobials are renally excreted, the lack of renal dosage adjustment is known to be a major risk, though CIE can be caused even with appropriate renal adjustment.[9] Brain imaging studies of the three patients in our cases were all within normal limits, and the latency of the symptoms and days to improvement

after discontinuation were consistent with previous reports.

In our three cases, common clinical features such as "altered mental status that can be misdiagnosed as a psychogenic condition", "pain", "palilalia (ouch, ouch, ouch...)", and "refusal of examination/medication" were newly observed (Table). These symptoms are reminiscent of those reported as higher functions involving inhibitory neural circuits. In a previous report, 90% of patients improve[6]. Although emergency dialysis and use of antiepileptic drugs may shorten the time to improvement, meta-analysis has not reached a clear conclusion, and discontinuation of cefepime is of critical importance[6)9)]. It is considered to be a reversible condition that basically resolves spontaneously[9)]. The clinical course of antimicrobial-associated encephalopathy can be found in my another review (in Japanese)[9)].

2.Characteristic EEG, Tri-HNC, in Cefepime-induced Encephalopathy

The EEGs of the three cases were all characteristic, and we coined the term tri-phasic wave-like generalized periodic discharges with a high negative component (Tri-HNC; Fig. 2a, b, c). For quantitative evaluation, we detected the position of the peak by semi-automatic method and calculated the negative/positive ratio, the number of occurrences of Tri-HNC (c/s), and the duration (s) of the entire Tri-HNC (Fig. 2d, e). In the original paper[8)], we also analyzed the recovery course of EEG using Fourier analysis, but this is omitted due to space limitation in this paper.

3.Neural Mass Modeling

Liley et al.'s neural mass modeling[5)] is a mean-field model that neurons in the cerebrum, which number in the order of 1 to 10 billion in humans, are represented by one excitatory (e) and one inhibitory (i) neuron, each of which projects to the other. The projection from a to b is denoted by the subscript ab. For example, the number of synapses that project from excitatory to inhibitory is N_{ei}, and the current that self-projects from excitatory to excitatory is I_{ee} (Figure 3a, b).

Without going into details, the differential equations used are simple enough to be written in two lines.

$$\tau_e \frac{dV_e}{dt} = V_e^{\text{rest}} - V_e(t) + \Psi^e_{\text{AMPA}} I_{ee}(t) + \Psi^e_{\text{GABA}} I_{ie}(t) + \Psi^e_{\text{AMPA}} I_{ne}(t)$$

$$\tau_i \frac{dV_i}{dt} = V_i^{\text{rest}} - V_i(t) + \Psi^i_{\text{AMPA}} I_{ei}(t) + \Psi^i_{\text{GABA}} I_{ii}(t) + \Psi^i_{\text{AMPA}} I_{ni}(t)$$

Brief explanations are as follows:

(1) The membrane potential $V(t)$ of a neuron is a function of time t and approaches the resting membrane potential V^{rest} with time constant τ.
(2) The current $I(t)$ and conductance Ψ define the rate of change of the membrane potential.

(The final term is a noise term that assumes projections from other regions such as the thalamus.) The number of synapses and the membrane potential at that moment determine the current and conductance of neurotransmitters (AMPA, GABA). See the original paper[8] for details.

The model is very simple as the only variable is the number of synapses (other than that, we just substituted constants as initial conditions based on previous reports).

4.Estimation of underlying pathological mechanism by computer simulation

Tri-HNC was reproduced by setting the number of synaptic inputs (variable) as shown in Figure 3b to an appropriate value. The negative/positive ratio described above is equivalent for the three cases and two sets of variables (Fig. 3d), suggesting that the most prominent feature of Tri-HNC is described by this simulation.

It was also shown that the basal rhythm slowed down when both excitatory and inhibitory inputs were reduced while maintaining the E/I balance (Fig. 3e). This fact may explain the clinical course of recovery and may also reproduce individual differences in response to benzodiazepines[8].

The simulation also allows for manipulations that cannot be observed or permitted clinically, such as increasing the excitatory input to 200% of the normal level. A detailed investigation of the conditions under which Tri-HNC is generated showed that Tri-HNC appears at the critical point (phase transition condition) when the E/I balance collapses and the basal activities disappear (Fig. 3f). Furthermore, this phenomenon cannot be explained by changes in a single variable alone, suggesting that the basis for the generation of Tri-HNC is at the level of neural circuits. Given the $GABA_A$ receptor antagonist effect of cefepime, the underlying mechanism of CIE is presumed to involve autoinhibition of inhibitory neurons.

In addition to CIE, anti-GAD antibody-associated encephalitis (or anti-GABA receptor antibody-associated encephalitis) also shows Tri-HNC with different time frequencies[8]. We hypothesize that there is a common pathophysiological basis when the GABAergic inhibitory mechanism is disrupted, and that Tri-HNC is a phenotype on examination[8)9)].

II. Discussion

In this paper, we performed *in silico* simulation using neural mass modeling to reproduce Tri-HNC, which characteristically appears in encephalopathy induced by cefepime, a $GABA_A$ receptor antagonist. The simulation also suggested that E/I imbalance due to auto-inhibition (synaptic inputs from interneuron to interneuron) dysregulation contributed to the generation of Tri-HNC.

1. Scope of the simulation

In our simulations, we were able to produce triphasic wave-like waveforms with a high negative component (negative/positive ratio ≥1) and spindle-like waveforms, though we could not reproduce conventional triphasic wave-like waveforms with a high positive component (negative/positive ratio <1), seen in such as hepatic encephalopathy[8] .

We conceive that conventional triphasic wave-like waveforms can be reproduced by increasing the number of variables; however, the fewer variables, the better, since models are most valuable in simplifying complex phenomena. In this study, we reproduced Tri-HNC with a small number of variables, and it is worthwhile to quantify the morphology of the "triphasic wave", which has not been focused on so far, and to estimate the underlying pathological mechanism suggested by the morphology. Since EEG can be used as a translatable brain marker, we hope the mechanism inferred in this paper will be further verified by biological experiments.

For details of the differential equations and biophysical models used in this paper, I recommend the recently published book “Computational Psychiatry”, which is an excellent primer in Japanese[4].

2.New Consultation-Liaison Psychiatry: Researching the Boundaries with Other Fields

Clinicians are less likely to judge a triphasic wave as a "typical" triphasic wave if it has a high negative component (i.e., Tri-HNC; odds ratio 0.09: 0.02-0.22) and judge it as "atypical"[2]. However, the clinical and basic neuroscientific significance of this morphology has not been investigated.

This study was initiated when a psychiatric consultation-liaison team experienced several patients with CIE and noticed that the clinical course was different from that of "so-called delirium", but that the patients were somewhat homogeneous, with a common finding of Tri-HNC on EEG. Since cefepime inhibits $GABA_A$

receptors and the EEG abnormalities were generalized, we thought that neural mass modeling could be applied. Fortunately, we succeeded to simulate the morphology with a kind input from an expert of seismology. Retrospectively, we feel that this is an ideal form of consultation-liaison psychiatry that aims to study the boundary (= the cutting edge) with other fields (incidentally, Tri-HNC itself is a phenomenon at the boundary of phase transition, as shown in Fig. 3f).

Conclusion - Outlook

Type I antimicrobial-associated encephalopathy, including CIE, is likely to have psychiatric symptom changes due to slightly altered mental status before seizures. Although aphasia has been reported as a characteristic symptom of CIE, palilalia (repetitive speech) may exist as a preliminary stage. Since the patient with CIE experiences a much greater deterioration in eye and verbal responses than in their motor responses, these symptoms may be misdiagnosed as a psychogenic condition, if the clinician overlook flashy EEG abnormalities (Tri-HNC).

Recalling CIE as a differential diagnosis by Tri-HNC and clinical course allows for subsequent personalized care. Proactive diagnosis of a self-limiting condition that may resolve spontaneously encourages discontinuation or modification of medications, which is very beneficial from the standpoint of patient safety, and also has medical economic significance by preventing excessive examinations.

In terms of research, focusing on pathophysiological conditions with clear pharmacological causal relationships has led to the establishment of new disease concepts, such as NMDA receptor-related encephalitis. Given the rapid progress of basic neuroscience , if psychiatrists can extract a homogeneous group from a heterogeneous group of patients through careful clinical observation in the viewpoint of psychopathology and pharmacology, we can step forward together with findings in surrounding fields.

This paper is a revised version of a recent paper published in *PCN*[8] by one of the authors in Japanese at the request of the editorial board, with additional comments on the significance and prospects of the paper.

There are no conflicts of interest to disclose with respect to this paper.

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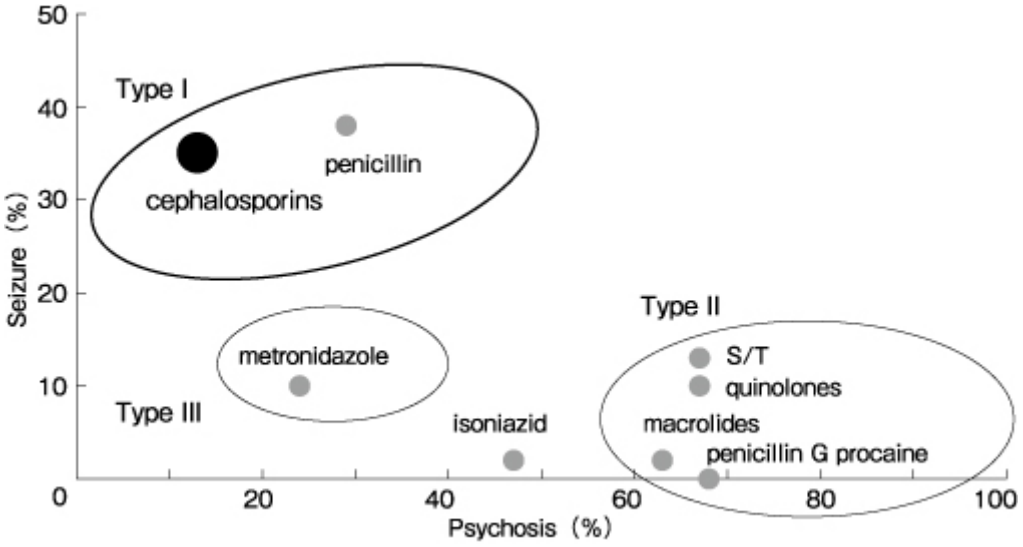

Figure 1 Types of antibiotic-associated encephalopathy (AAE)
Cefepime is a fourth-generation cephalosporin that inhibits $GABA_A$ receptors. Cefepime-induced encephalopathy is classified as a type I AAE with few psychosis and many epileptic seizures, and often associated with impaired renal function. It is basically considered to be a reversible condition that resolves spontaneously several days after discontinuation of cefepime, further studies are required. The clinical course of antimicrobial-associated encephalopathy can be found in my another review (in Japanese)[9].(Quoted and modified from Ref. 1 and Ref. 9)

Table. Summary of three cases of cefepime-induced encephalopathy

Age	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	33	No	Pneumonia	AMS (E1V2M4) Palilalia Refusal of examination	5	Observation	4
94	Female	38.3	14	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/1.73m^2]; DZP, diazepam 5mg; PHT, phenytoin 250mg
(Quoted from Ref. 8)

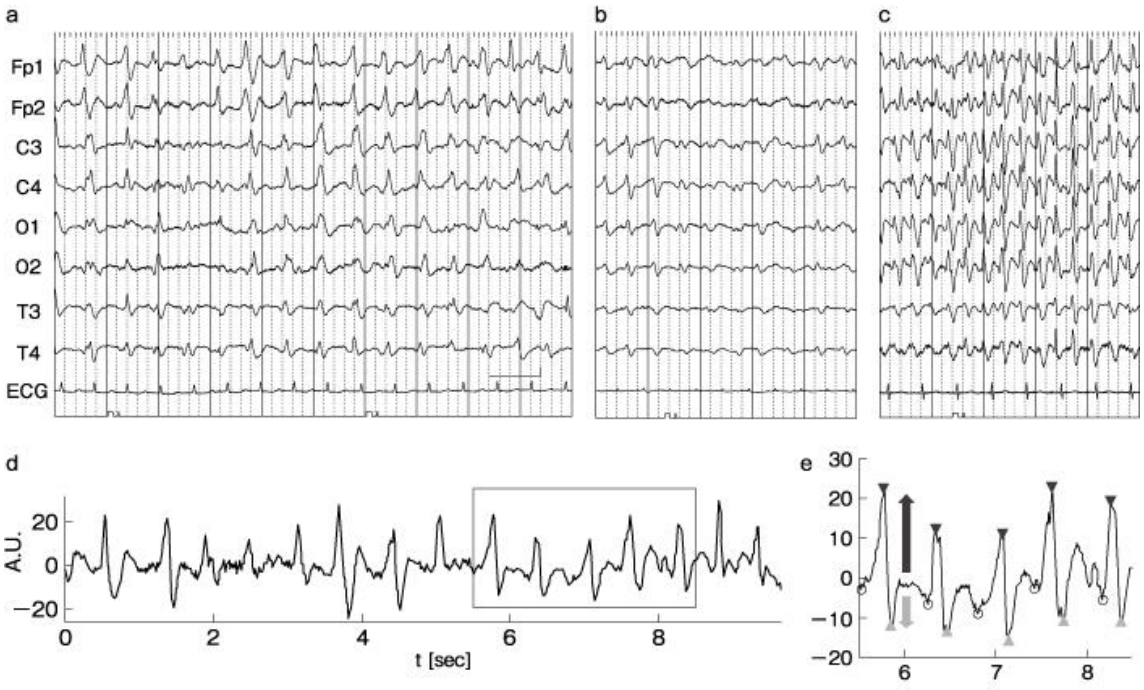

Fig. 2 Three self-tested cases of cefepime encephalopathy.
a-c: EEGs of 64-year-old woman, 44-year-old man, and 94-year-old woman, respectively, shown in Table 1. Triphasic wave-like generalized periodic discharges with a high negative component (Tri-HNC) are observed in all three patients.

*This is a commentary on the article published in PCN.

d, e. A part of Fp1 in Fig.2a is extracted and the peak positions are identified semi-automatically. Ratio of negative component (upward, black arrow) and positive component (downward, gray arrow) are calculated. (Quoted and modified from Ref. 8)

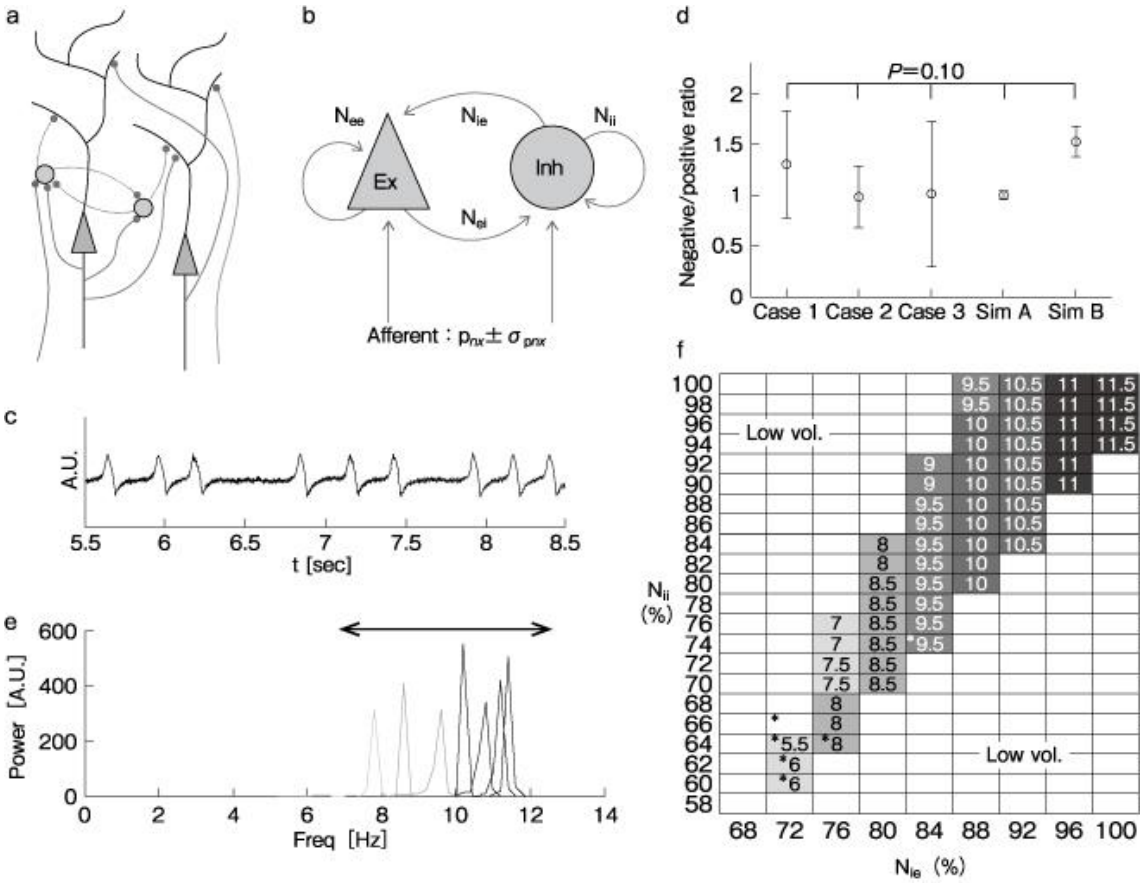

Figure 3 Simulation results using neural mass modeling.

a, b: Conceptual diagram of neural mass modeling. Excitatory (Ex, e) and inhibitory (Inh, i) synapses project to each other. In this study, only the 4 numbers of synapses were used as a variable. c, d: The Tri-HNC was reproduced by giving appropriate values. The negative/positive ratio was statistically not significant for the three cases and two sets of variables, suggesting that the most prominent feature of the high negative component was expressed. e: When both excitatory and inhibitory inputs were reduced while maintaining E/I balance, the basal rhythm slowed down correspondingly. Interestingly, the frequency generated as the basal activity almost coincides with the alpha band. f: When examining which variables contribute to the

generation of Tri-HNC, we find that the condition (indicated by an asterisk (*)) under which Tri-HNC appears is the critical point where the E/I balance disrupts and the basic activity disappears. Experimental increase of N_{ee} and N_{ei}, namely increase E in E/I balance, also reproduce Tri-HNC (data not shown). When the E/I balance is greatly disrupted, the waveform goes Low Vol. (Quoted and modified from Ref. 8)