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Tongue Tremor After Levetiracetam Administration

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Dear Editor,

Levetiracetam is a widely used antiepileptic drug. It is considered to be a well-tolerated drug, but has been associated with some side effects including somnolence, dizziness, infection, depression, and behavior problems.

A 69-year-old female was admitted to our hospital due to fever and drowsy mentality. At 61 years of age, the patient had been diagnosed with early-onset Alzheimer's disease and received treatment with donepezil and memantine. The patient had no history of epilepsy or medication-induced parkinsonism.

At the time of admission, a urinary tract infection was found and so the patient was treated with ciprofloxacin (400 mg/day). After 14 days her body temperature and biomarkers of infection had noticeably normalized. However, the general condition of the patient had gradually deteriorated, and she had developed repetitive eyeball deviation to the left. Brain MRI showed severe global frontoparietotemporal atrophy. Interictal EEG showed a diffuse theta rhythm, and ictal EEG showed rhythmic delta activity over the right frontal area. Status epilepticus was suspected, and so the patient was treated with intravenous phenytoin (900 mg/day) and valproate (800 mg/day). The seizures did not recur after loading of the antiepileptic drug, and she was subsequently maintained on only phenytoin (300 mg/day). The findings of laboratory tests including serum chemistries and complete blood count were normal. The serum level of phenytoin was 6.94 mg/L.

Phenytoin was reduced to 200 mg/day and levetiracetam was added at 1,000 mg/day orally for drug switching. No other medication added, including a dopaminergic antagonist. One day after the administration of levetiracetam, the patient showed fast (>13 Hz) and high-amplitude tongue tremor for the first time. The concomitant EEG showed diffuse theta activity and no epileptiform discharge.

The tongue tremor disappeared at 2 days after withdrawing levetiracetam. Lamotrigine was added to phenytoin after 3 days, and no more tongue tremor was observed when she received lamotrigine at up to 200 mg/day.

This report describes a patient with newly onset tongue tremor that developed while switching from phenytoin to levetiracetam. Considering the temporal relationship between tremor and drug administration and withdrawal, her condition was attributed to levetiracetam. According to the Adverse Drug Reaction Probability Scale,[1] this was considered a probable adverse drug reaction to levetiracetam. There are few reports on extrapyramidal symptoms induced by levetiracetam, with our literature review revealing only three cases (Table 1).[2-4]

Levetiracetam exhibits relatively minor pharmacodynamic interactions with other antiepileptic drugs. It acts by inhibiting neuronal hypersynchronization by binding to synaptic vesicle protein 2A. Also, acutely applied levetiracetam may modulate neuronal activity via inhibition of presynaptic calcium channels and the postsynaptic AMPA-type glutamate receptor. Levetiracetam interacts with dopamine neurotransmission through these ion channels. A possible explanation is that acute exposure to levetiracetam results in dopamine re-

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Table 1. Summary of previously reported cases of dyskinesia induced by levetiracetam

Study	Age (yr)	Sex	Levetiracetam dosage	Other medications	Concomitant neurological disease	Clinical features
Zesiewicz et al.[2]	58	M	750 mg/day	Olanzapine, donepezil, paroxetine, trazodone, furosemide, oxybutynin, gabapentin	Huntington disease, dementia, depression	Lethargy, parkinsonism (resting tremor and shuffling gait)
Gatto et al.[3]	36	M	1,000 mg/day	Olanzapine, clonazepam, amantadine, paroxetine, coenzyme	Huntington disease	Dysarthria, axial and mandibular rigidity
Yim et al.[4]	28	F	1,000 mg/day, intravenous	None	Spinal cord glioblastoma, status epilepticus	Choreoathetoid movements in face and bilateral limbs

F, female; M, male.

ceptor dysregulation and leads to dyskinesia.[4] Also, genetic variations may determine individual differences in the effect of dopaminergic activity of levetiracetam.[5]

The other mechanisms involved could be interactions between drugs such as phenytoin, donepezil, and levetiracetam. Most cases of anticonvulsant-induced dyskinesia have been reported in association with first-generation antiepileptic drugs.[6] Phenytoin is the most commonly reported drug, but the pathogenesis remains unknown. One theoretical possibility is that phenytoin causes dyskinesia through blockage of dopamine receptors and inhibition of dopamine uptake, resulting in supersensitivity of dopamine receptors. Although phenytoin was in stable use by the present patient and underwent dosage reduction, a pharmacodynamic interaction with phenytoin and levetiracetam also resulted in a synergistic effect on the central dopaminergic pathway.[6]

Ethics Statement

This study was approved by the Institutional Review Board of Kyung Hee University Hospital (IRB No 2021-06-004), with a waiver of the requirement for informed consent.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-245.
2. Zesiewicz TA, Sanchez-Ramos J, Sullivan KL, Hauser RA. Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2005;28:188-190.
3. Gatto EM, Roca CU, Etcheverry JL, Fadel D. Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2006;29:303-304.
4. Yim SH, Choi YH, Heo K, Cho KH. A case of dyskinesia after levetiracetam administration. *BMC Neurol* 2019;19:292.
5. Helmstaedter C, Mihov Y, Toliat MR, Thiele H, Nuernberg P, Schoch S, et al. Genetic variation in dopaminergic activity is associated with the risk for psychiatric side effects of levetiracetam. *Epilepsia* 2013;54:36-44.
6. Zaatreh M, Tennison M, D'Cruz O, Beach RL. Anticonvulsants-induced chorea: a role for pharmacodynamic drug interaction? *Seizure* 2001;10:596-599.