

Pathophysiological crosstalk between migraine aura and epilepsy: Effect of lomerizine hydrochloride

Kazuki Fujita (✉ mm08089kf@gmail.com)

Saitama Neuropsychiatric Institute

Mamoru Shibata

Tokyo Dental College Ichikawa General Hospital

Yuichi Maruki

Saitama Neuropsychiatric Institute

Fumihiko Sakai

Saitama International Headache Center

Case Report

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Abstract

Background: Migraine and epilepsy are comorbid diseases. Although they are independent clinical entities, we experienced a case of migraine complicated with epilepsy that exhibited unique temporary changes in clinical manifestation.

Case presentation: A 29-year-old woman previously diagnosed with both migraine with aura and epilepsy visited our hospital complaining of unusual headaches. In her 20's, the prodromal symptoms changed from typical scintillating scotoma lasting 20 minutes to moving lights against déjà-vu scenery lasting 1-2 minutes. Then, loss of consciousness and urinary incontinence after headaches began to occur. Even generalized convulsion occurred. Considering the clinical symptoms, her headache was thought to be changed from migraine with typical aura to headache attributed to epileptic seizure. Administration of lomerizine hydrochloride decreased her headache attacks, urinary incontinence and loss of consciousness, and seizure.

Conclusions: We report a patient with migraine and epilepsy who was successfully treated with lomerizine hydrochloride, an analog of flunarizine hydrochloride widely used in Japan. There may be mutual crosstalk between migraine and epilepsy. Lomerizine hydrochloride may have the efficacy of alleviating migraine and epilepsy.

Background

Migraine and epilepsy have common features such as accompanying aura and similar treatments to prevent symptoms [1]. They may occur as a comorbid disease [2]. Distinguishing between migraine attacks and seizure-associated headache episodes is sometimes difficult, particularly in complex cases. For such cases, the diagnosis of "Migraine aura-triggered seizure" is often used according to the diagnostic criteria by the International Classification of Headache Disorders 3rd edition (ICHD-3) (1.4.4). Migraine aura-triggered seizure is defined as a subtype of migraine in which the seizure is considered to be triggered by the aura of migraine. A comment was added in ICHD-3 that migraine and epilepsy are prototypical examples of paroxysmal brain disorders. This phenomenon is referred to as migralepsy, is a rare event, and was originally described in patients with migraine with aura. Although migraine and epilepsy are independent clinical entities, we experienced a case of migraine complicated with epilepsy that exhibited unique temporary changes in clinical manifestation. To the best of our knowledge, no report has been published about patients with a combined state of migraine and epilepsy treated with lomerizine hydrochloride.

Lomerizine hydrochloride was used in this patient to prevent the aura of migraine. Lomerizine hydrochloride was developed as an analog of flunarizine hydrochloride and as a blood-brain barrier (BBB)-permeable Ca^{2+} channel blocker designed to reduce side effects in the extrapyramidal system. We report a patient with migraine and epilepsy who was successfully treated with lomerizine hydrochloride.

Our case suggested crosstalk between migraine and epilepsy and that lomerizine hydrochloride is effective for prevention of not only migraines but also epilepsy.

Case Presentation

A 29-year-old woman visited our hospital complaining of an unusual headache. She had no family history of either headache or epilepsy. She was born following a normal gestational period and delivery and had no history of febrile seizures. At the age of 3 years, she had lost consciousness while watching TV. She was diagnosed with epilepsy and started valproic acid. When she was 17 years old, she began to have attacks of pulsating headaches with nausea, vomiting, and photophobia, which were preceded by spreading scintillating scotoma lasting for 20 minutes. Visual aura was sometimes followed by short-lasting aphasia. At the age of 19 years, a neurologist diagnosed her with migraine with typical aura, and she started taking triptan, which relieved the severity of the headaches. The pattern of prodromal symptoms before the headaches changed during her early 20's. The duration became shorter, from 20 minutes to 1–2 minutes. Triggering factors were menstrual period, tiredness, insomnia, hunger, relief from tension, careless withdrawal of the anti-epileptic drug, and viewing a smartphone or computer. She also began to experience a visual aura of deformed images of Chinese characters repeatedly appearing against the specific déjà-vu scenery. In addition to the headaches, she noticed that her eyes were pulled upward diagonally toward the direction of the visual image. She was able to bring her eyes back to the normal position by herself, but her eyes did not stay at the normal position and were pulled upward again. What she wrote during the prodrome and headache were illegible, and what she talked to her family about during the episode did not make sense. She showed no motor or systemic sensory symptoms. Repeated cranial magnetic resonance imaging and electroencephalogram (EEG) were normal. When she was 25 years old, she developed loss of consciousness and urinary incontinence preceded by the usual symptoms of visual and language disturbances and headaches. This type of episode happened once a year. At the age of 27 and 28 years, she developed generalized tonic convulsions after the headache following the usual visual and verbal symptoms. She then visited our hospital.

At the time of the initial visit to our hospital, the only medication she was taking was valproic acid 600 mg per day. The previously independent attacks of epilepsy and migraine with aura seemed to have converted into a single series of symptoms. The nature of her headaches continued to be the same as before, even after the prodromal visual symptoms had transformed from typical visual auras to complex visual symptoms. The provisional diagnosis at the initial visit based on the clinical history was “migraine aura-triggered seizure” according to ICHD-3. Considering the severity of the headache and comorbidity of epilepsy, prophylactic therapy was started. Because she was already taking valproic acid to treat the epilepsy, lomerizine hydrochloride 20 mg daily was added. EEG showed paroxysmal waves predominantly in the bilateral parietal to occipital regions after photic stimulation and before hyperventilation. Based on EEG, the short duration of the visual symptoms, and the lateralizing sign before the headache, we considered that the cause of the headaches in our patient had changed from migraine with typical aura to headache attributed to epileptic seizure with the focus in the occipital lobe.

After administration of lomerizine hydrochloride, attacks of headache with preceding short-lasting visual and speech disturbances markedly decreased to once a month. Headaches accompanying loss of consciousness with urinary incontinence and tonic seizure disappeared. During the 20 months following administration of lomerizine hydrochloride, she developed loss of consciousness only once.

Discussion

This case indicates that the pathophysiology of migraine and epilepsy may involve bidirectional crosstalk, and the symptoms of one may modify the symptoms of the other. In addition, lomerizine hydrochloride may modify the process of both migraine and epilepsy.

The pathophysiological relationship between migraine and epilepsy has long been discussed clinically. Our patient required careful consideration because she presented with various symptoms of both migraine and epilepsy. Her initial symptom was epilepsy at the age of 3 years, which indicates that she has a seizure disorder. Since the age of 17 years, she presented with migraine with typical aura, which was often prolonged and associated with aphasia. Later, at the age of 25 years, migraine aura was followed by loss of consciousness and urinary incontinence, and even generalized tonic-clonic seizures occurred. Epilepsy and migraine with aura became a series of symptoms when the visual symptoms became shorter in duration. No changes in migraine-like headaches occurred after the change in the preceding visual symptoms. Our provisional diagnosis at the time of her initial visit was “migraine aura-triggered seizure” according to ICHD-3. However, unique features of this patient are the change in the pattern of the prodromal symptoms and also seizures with urinary incontinence following the headaches. Neurological symptoms preceding the headaches changed from the usual typical aura to a short-lasting aura, which included complaints of *deja-vu* scenery, a common feature of epileptic hallucinations that usually helps distinguish epilepsy from migraines [3].

Both migraine and epilepsy are associated with brain hyperexcitability, with migraine being initiated by cortical spreading depression (CSD). Pathophysiologically, migraine, and epilepsy do not occur simultaneously, but clinical observation of our patient suggested that they may occur sequentially in migraine aura-triggered seizure [4]. Seizures may trigger trigeminovascular pain mechanisms, as migraine is triggered by CSD [5]. One theory for migraine is the central sensitization mechanism. This theory proposes altered processing of sensory input in the brainstem, principally the trigeminal nucleus caudalis [6]. Recent research has suggested the possibility of a similar mechanism for headache in epilepsy [7].

Lomerizine hydrochloride was effective for this patient and may have been effective both for migraine and epilepsy. After administration of lomerizine hydrochloride, the first headache attack followed by loss of consciousness and urinary incontinence did not occur until 1.5 years later, and the frequency of headaches due to either migraine or epilepsy decreased significantly from once a month to twice a year. Lomerizine hydrochloride is a voltage-dependent L- and T-type Ca^{2+} channel blocker that crosses the BBB and is recommended as one of the first-choice drugs for migraine prevention in the Clinical Practice Guideline for Chronic Headache 2013 by the Japanese Society of Neurology [8]. Lomerizine hydrochloride

belongs to the same class of diphenylpiperazine-type Ca^{2+} channel antagonists as flunarizine hydrochloride, which was withdrawn by the government of many countries because of the adverse events of parkinsonism [9]. Lomerizine hydrochloride, which was developed to replace flunarizine hydrochloride, inhibits cortical hypoperfusion and expression of c-Fos-like immunoreactivity induced by spreading depression in rats. This activity of lomerizine hydrochloride is mediated by blockade of Ca^{2+} entry, preventing excessive Ca^{2+} influx into neural cells [10]. Lomerizine hydrochloride may inhibit CSD in migraine. Lomerizine hydrochloride 10 mg daily reduces the frequency and severity of migraine attacks after 8 weeks in 64% of patients [8], and adverse events are similar to placebo, indicating the safety of the drug. Moreover, flunarizine hydrochloride was reported to have some effect for the treatment of epilepsy [11]. Our experience lends support to the tenet that lomerizine hydrochloride may be efficacious in alleviating migraine and epilepsy by suppressing brain hyperreactivity.

Conclusions

We report a patient with migraine and epilepsy who was successfully treated with lomerizine hydrochloride. Migraine and epilepsy may involve mutual crosstalk, and the symptoms of one may modify the symptoms of the other. Lomerizine hydrochloride may have the efficacy of alleviating migraine and epilepsy.

Abbreviations

ICHD-3 International Classification of Headache Disorders 3rd edition, BBB blood-brain barrier, EEG electroencephalogram, CSD cortical spreading depression

Declarations

Acknowledgments

None.

Authors' contributions

Dr. Kazuki Fujita is responsible for writing the first draft, editing the manuscript and approval of the final version of the manuscript. Dr. Mamoru Shibata and Dr. Fumihiko Sakai contributed in writing and editing the manuscript and approval of the final manuscript. Dr. Yuichi Maruki contributed in editing the manuscript and approval of the final manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

Data is available with the corresponding author upon request.

Ethic approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

All authors declare no conflicts of interest.

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