Acta Epileptologica

CASE REPORT Open Access

Two cases of childhood absence epilepsy who showed seizure disappearance after ethosuximide drug eruption

Takuji Nakamura[1,2], Keiko Uda[1], Muneaki Matsuo[1] and Masafumi Zaitsu[2*]

Abstract

Background: Recent studies suggest potential roles of immune response in the pathophysiology of epilepsy. Anti-seizure medications (ASMs) are known to have side effects of drug eruption caused by immune responses. A few reports in adults have demonstrated disappearance of seizures after an ASM drug eruption episode. In this paper, we described 2 cases of childhood absence epilepsy (CAE) who showed seizure disappearance after ethosuximide (ESM) drug eruption, suggesting the possibility that the epilepsy disappears due to immune responses to ASM.

Case presentation: Case 1 was an 8-year-old girl diagnosed with CAE. She was treated with valproate acid (VPA) initially, and then ESM was administered as an additional treatment. Her epileptic seizure disappeared 4 days after initiation of ESM. However, drug eruption appeared 1 week after the administration of ESM. Even after discontinuation of ESM administration, she maintains no seizure after the drug eruption. Case 2 was a 5-year-old boy diagnosed as CAE. He was treated with VPA initially, and ESM was administered additionally. Drug eruption appeared 1 month after the administration of ESM. Even after ESM was terminated, he maintained seizure freedom after the appearance of eruption.

Conclusions: Epileptic seizures may have been suppressed due to the immune responses caused by ASM eruption. Further studies are needed to elucidate the pathophysiologic effects of drug eruption on epilepsy through immune responses.

Keywords: Childhood absence epilepsy, Drug eruption, Ethosuximide, Seizure disappearance

Background

Recent studies have suggested potential roles of immune response and neuroinflammation in the pathophysiology of epilepsy [1–4]. On the other hand, anti-seizure medications (ASMs) are known to have side effects of drug eruption mediated by an immune response [5–7], which necessitates the discontinuation of the ASM. In a majority of such cases, the seizure episodes might recur. However, a few reports in adults demonstrated disappearance of seizures after an ASM drug eruption episode [8]. In this paper, we report 2 cases of childhood absence epilepsy (CAE) who showed disappearance of epilepsy after occurrence of an ethosuximide (ESM) drug eruption, suggesting the possibility that the epilepsy may disappear due to the immune response to an ASM.

Case presentation

Case 1

An 8-year-old girl had absence seizures accompanied by automatism, induced by hyperventilation. She had more than 10 absence seizures a day. Her electroencephalogram (EEG) showed a 3-Hz generalized spike-and-wave pattern, which occurred frequently with a duration of

*Correspondence: zaitsu.masafumi.hr@mail.hosp.go.jp

[2] Department of Pediatrics, National Hospital Organization Ureshino Medical Center, 4279-3 Shimojuku Kou, Ureshino City, Saga 843-0393, Japan
Full list of author information is available at the end of the article

seconds to tens of seconds (Fig. 1a). Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed no abnormalities. Hematological, blood chemistry and blood gas analyses did not reveal abnormal findings. We did not analyze susceptibility genes related to CAE [9]. She was diagnosed as CAE and was initially treated with valproic acid (VPA, 10 mg/kg per day) [10, 11]. The clinical course of case 1 is shown in Fig. 2a. As her epileptic seizures did not completely resolve, ESM (10 mg/kg per day) was added. One week later, the patient showed complete resolution of seizures, but she also developed fever, rashes, and conjunctival congestion. The rashes were non-pruritic and did not have a tendency to fuse. With a suspicion of drug eruption, ESM was discontinued and oral steroid (prednisolone, 0.5 mg/kg per day for 3 days) and antihistamine were administered. Thereafter, her symptoms, such as fever, rashes, and conjunctival congestion, improved immediately. We anticipated recurrence of the seizures after ESM discontinuation, but this did not occur. EEG recording at 4 months after the ESM drug eruption showed no abnormal pattern (Fig. 1b). The drug eruption

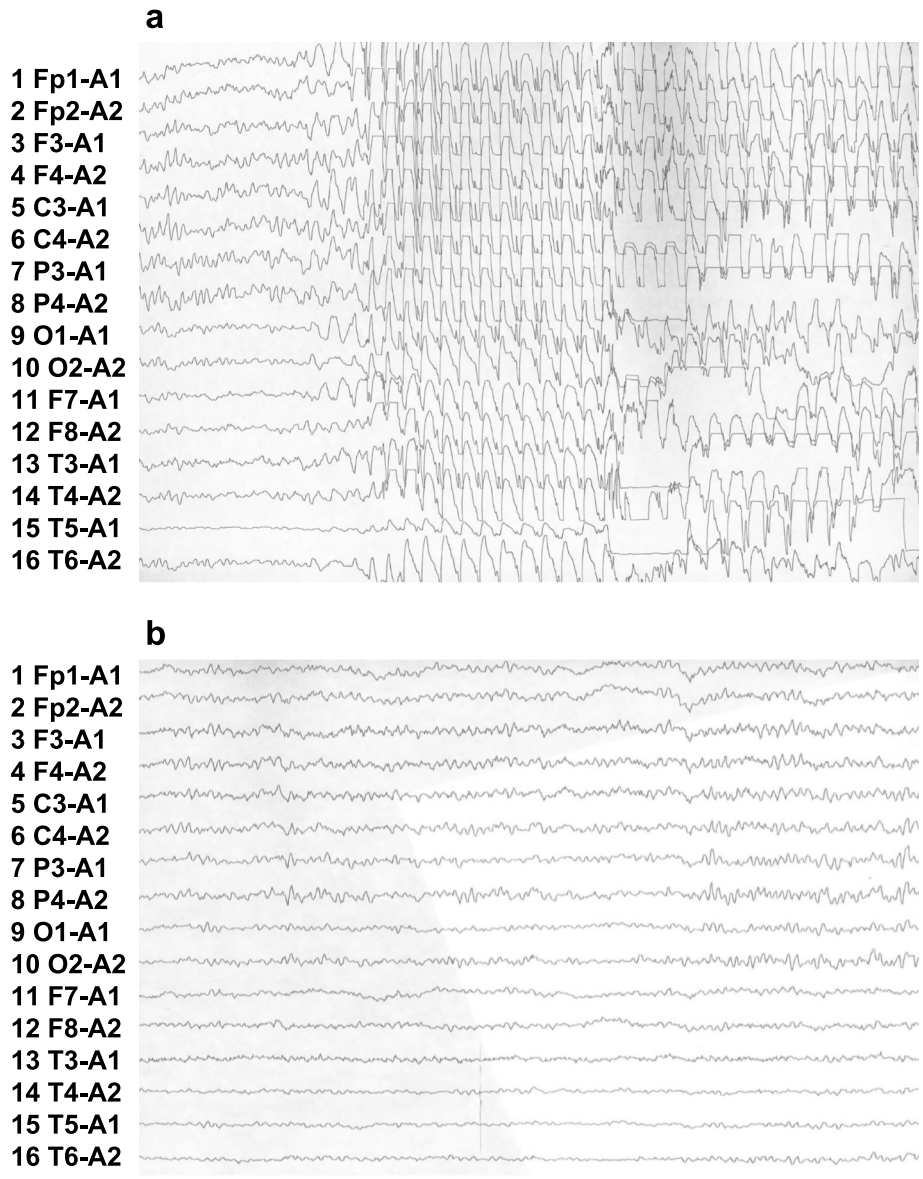

Fig. 1 The electroencephalograms of case 1. The electroencephalogram at diagnosis (**a**) showed a generalized spike-and-wave discharge at 3 Hz, and the electroencephalogram at 4 months after drug eruption (**b**) showed no abnormal pattern

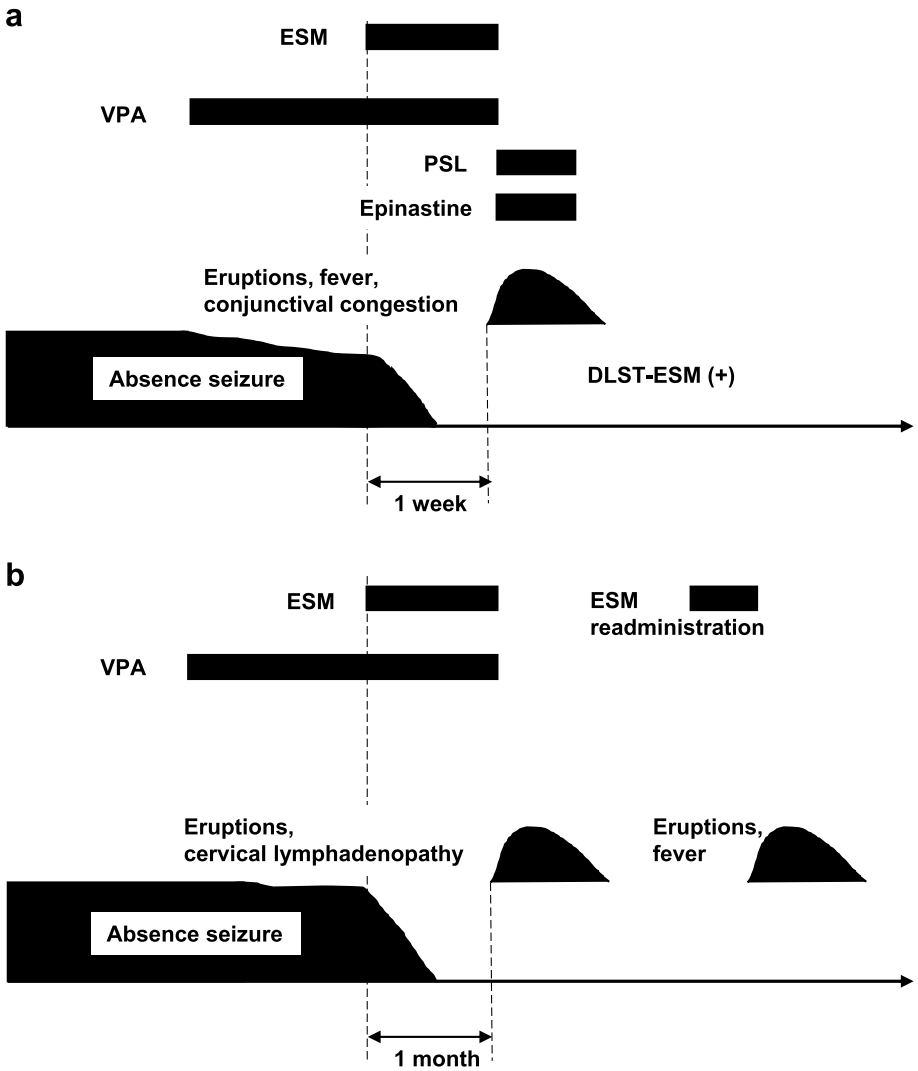

Fig. 2 The clinical courses of case 1 (**a**) and case 2 (**b**). DLST, drug-induced lymphocyte stimulation test; ESM, ethosuximide; VPA, valproic acid; PSL, prednisolone

was suspected to be caused by the drug-induced hypersensitivity syndrome. However, the diagnostic criteria were not met and human herpes virus 6 DNA was not detected. On the other hand, the drug-induced lymphocyte stimulation test (DLST) against ESM showed positive result. The patient was followed up for 2 years after appearance of the drug eruption, during which no absence seizures occurred.

Case 2

Case 2 was a 5-year-old boy who had absence seizures. EEG recording showed a 3-Hz generalized spike-and-wave pattern, which lasted for several seconds and appeared frequently. No abnormalities were revealed by brain MRI, MRA, and blood chemistry test. He was also not tested for CAE-related susceptibility genes. He was diagnosed as CAE and was initially treated with VPA (10 mg/kg per day) (Fig. 2b). However, ESM (10 mg/kg per day) was added because VPA was not effective. At 2 weeks after addition of ESM, his seizures completely resolved, but he also developed amorphous rashes and cervical lymphadenopathy. With a suspicion of adverse drug reaction, both ESM and VPA were discontinued. Thereafter, the symptoms improved immediately, and the patient remained seizure-free afterward. Nevertheless, ESM administration was resumed due to the concerns of his parents on seizure recurrence. After re-administration of ESM, the patient developed fever and rashes, which were clinically diagnosed as drug eruption caused by the re-administration of ESM, so the DLST test was

not performed. After the episode of drug eruption, the patient was free from attacks of absence seizures even after discontinuation of ESM. Three months after the drug eruption, EEG recording showed no abnormal pattern. The patient was followed up for two years and no absence seizures occurred.

Discussion

Several recent clinical and preclinical studies have suggested a potential role of immune response and neuroinflammation in the pathophysiology of epilepsy and epileptogenesis, including absence epilepsy [1–4]. Here we described 2 cases of CAE who showed epilepsy disappearance after occurrence of drug eruption, probably due to an immune response to ESM.

CAE, which is the most common form of epilepsy in children, depends on age and is one of the benign seizure disorders. VPA and ESM have been used as the ASMs for CAE [10, 11], but similar to the other ASMs, they have side effects, such as drug eruption. In general, occurrence of drug eruption in CAE patients would necessitate discontinuation of the offending ASM; however, in most cases, there is a risk of seizure recurrence. Interestingly, Kakisaka et al. reported resolution of seizures after a drug eruption episode due to lamotrigine (LTG) in a 57-year-old woman who had seizures after a cerebral infarction [8]. LTG administration was able to control her seizures, but she had a drug eruption after 35 days. The eruption was promptly improved after discontinuation of LTG, and her epileptic seizures were not observed thereafter. The clinical courses of our 2 cases were similar to this previously reported case.

The mechanism of epileptic seizure disappearance after a drug eruption is unclear. The immune modulation in drug allergies may be involved in seizure suppression. In this report, the case 1 was tested positive for DLST against ESM, and seemed to have drug eruption caused by type-4 allergy [12]. In general, the type-4 allergic reaction is involved in ASM-induced drug eruption. When the ASM antigen is recognized by and binds to the major histocompatibility antigen (MHC), the drug-specific CD4+ and CD8+ T cells are activated. As a result, the activated CD4+ and CD8+ T cells produce inflammatory cytokines such as interleukin-8 (IL-8), IL-2 and IFN-γ [5, 13]. Although the details of the mechanisms are unknown, immunomodulation, such as regulation of cytokine production, might contribute to the suppression of the epileptic seizure.

Immune response to viral infections is another possible mechanism. In fact, several cases of West syndrome have been reported to have seizure disappearance following acute viral infections, such as exanthema subitum, rotavirus colitis, measles, and mumps, so direct immune reactions in response to several viral infections might be involved in seizure disappearance [14, 15]. Inflammation as an immune response in viral infection may be associated with the disappearance of seizures.

Several other factors are also suspected to contribute to the seizure disappearance in our 2 cases. One is the antiepileptic and anti-inflammatory effects of prednisolone administration (case 1). However, it is unlikely that short-term administration of steroids, which is not a high-dose therapy, would result in the disappearance of seizures. The other is the anti-seizure effect of ESM and/or VPA itself. This possibility cannot be completely denied. However, even considering these factors, the strong coincidence of seizure disappearance with the appearance of drug eruption suggests that drug eruption is a trigger for epileptic seizure disappearance.

Our case report had some limitations. First, video EEG, which is useful for observing the obscure symptoms of CAE [16, 17], was not performed in our 2 cases, thus we could not confirm the detailed association between unclear symptoms and EEG. Second, several susceptibility genes for CAE have been reported [9, 18, 19]. It has also been reported that certain gene variants may be involved in the responsiveness to the treatment of CAE [20]. Several genetic factors may play a role in the disappearance of seizures after drug eruption. In future studies, a genetic test should be performed to identify any genetic factors that may be involved in the disappearance of seizures after drug eruption.

Conclusions

In this report, we described 2 pediatric patients with CAE who showed seizure disappearance after ESM-induced drug eruption. Further studies are needed to elucidate the pathophysiology of the effects of drug eruption on epilepsy via immune responses.

Abbreviations

ASM: Anti-seizure medication; CAE: Childhood absence epilepsy; DLST: Drug-induced lymphocyte stimulation test; EEG: Electroencephalogram; ESM: Ethosuximide; HHV-6: Human herpes virus 6; IL: Interleukin; LTG: Lamotrigine; MHC: Major histocompatibility antigen; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; VPA: Valproic acid.

Acknowledgements

We thank the patients and their families for their consent to publish this report.

Authors' contributions

NT and UK collected the information of the two cases and drafted the manuscript. MM reviewed related articles and extracted the data. ZM conceived the study and revised the manuscript. All authors have read and approved the final manuscript.

Funding

The study was not supported by any funding.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committee of National Hospital Organization Ureshino Medical Center (No.18–13) and written informed consent has been obtained from the parents of patients prior to analysis.

Consent for publication
The written informed consent for publication was obtained from the parents of patients.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Pediatrics, Faculty of Medicine, Saga University, Saga, Japan. [2]Department of Pediatrics, National Hospital Organization Ureshino Medical Center, 4279-3 Shimojuku Kou, Ureshino City, Saga 843-0393, Japan.

Received: 25 April 2022 Accepted: 20 July 2022
Published online: 01 December 2022

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