LAMOTRIGINE-RELATED DISSEMINATED INTRAVASCULAR COAGULATION IS MEDIATED BY ANTICONVULSANT HYPERSENSITIVITY SYNDROME : A PHARMACOEPIDEMIOLOGICAL STUDY

Hayahito Ishikawa[1)], Masahiro Takeshima[2)], Hiroyasu Ishikawa[2)] and Kazuo Mishima[2)]

[1)]*Department of Neuropsychiatry, Japanese Red Cross Akita Hospital*
[2)]*Department of Neuropsychiatry, Akita University Graduate School of Medicine*

(received 27 July 2021, accepted 26 August 2021)

Abstract
The relationship between disseminated intravascular coagulation (DIC) and lamotrigine (LTG) use is a controversial topic. We hypothesized that DIC after LTG use is mediated by anticonvulsant hypersensitivity syndrome (AHS), based on our clinical experiences. To examine this hypothesis, a pharmacoepidemiological study was designed using the Japanese Adverse Drug Event Report database (JADER). Twenty-two cases of LTG-related DIC were identified by an exhaustive survey of JADER. AHS triad of fever, skin eruption, and internal organ involvement (indicated by liver dysfunction) were also investigated on each case. Fifty-nine percent of LTG-related DIC cases had the AHS triad. These results suggest that a distinct etiology, namely AHS or a phenomenon related to this syndrome, is the underlying mechanism of LTG-related DIC. LTG may induce DIC via AHS. More attention should be focused on the risk of DIC with LTG use.

Key words : lamotrigine, coagulopathy, anticonvulsant hypersensitivity syndrome, adverse event, pharmacoepidemiology

Introduction

The relationship between disseminated intravascular coagulation (DIC) and lamotrigine (LTG) use is a controversial topic. The first case of LTG-related DIC was reported in 1992 by Brodie[1)]. Subsequently, one or two isolated cases have been reported, including two cases presented by our group[2-6)]. In addition to case reports, other incidences of LTG-related DIC can be found in the literature[7-10)]. Although some medical professionals have suggested a causality between DIC and LTG use[2,3,5,6)], opposing opinions exist[1,10)]. LTG-related DIC is relatively rare ; therefore, it has been difficult to obtain sufficiently large patient sample sizes to examine causality.

Anticonvulsant hypersensitivity syndrome (AHS) is a potentially fatal multi-organ reaction induced by anticonvulsants and characterized by fever, skin eruption, and internal organ involvement (i.e., the so-called triad)[11)]. AHS has not been considered a DIC-relevant phenomenon[12,13)]. However, DIC can occur in the acute course of AHS induced by LTG, as we have previously reported[5,6)]. While previously reported cases of LTG-related DIC were not diagnosed with AHS, except for our two previ-

Corresponding author : Masahiro Takeshima
Department of Neuropsychiatry, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita-shi, Akita 010-8543, Japan
Tel : +81-18-884-6122
Fax : +81-18-884-6163
E-mail : m.takeshima@med.akita-u.ac.jp

ously mentioned cases, each symptom of the triad was described in these literature reports[2-4]. Thus, it is worth examining as a research hypothesis whether DIC following LTG use is mediated by AHS.

In Japan, physicians are obliged to report unlisted adverse events induced by drugs by law (an Act of the Pharmaceutical and Medical Device Agency, an Independent Administrative Agency) and via a system (the reporting system on safety information on drugs)[14]. Since DIC is an unlisted adverse effect of LTG, all cases of LTG-related DIC, in principle, have been registered and archived in the Japanese Adverse Drug Event Report database (JADER). A dataset obtained from JADER by an exhaustive search for LTG-related DIC reports could be regarded as a representative sample of Japanese patients. Therefore, we planned a pharmacoepidemiological study using JADER to test this research hypothesis.

Materials and Methods

Subjects

The subjects of this study were individuals for whom adverse event reports were registered in JADER. JADER is an open, public database that provides users with online search capabilities (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html). The current version of the system can be used to search for adverse events that emerged after 2005. We targeted DIC events registered in relation to LTG use. We searched for LTG-related DIC reports using JADER on March 18, 2017 and identified 22 cases.

In Japan, DIC is not listed as a side effect in the product information package inserts of LTG. As mentioned above, such unlisted adverse events must be reported by the discovering individual and subsequently uploaded to the JADER. Thus, the dataset obtained from JADER can be considered a representative sample of DIC incidences associated with LTG administration in Japan.

Methods

The major clinical information registered in the JADER for each case was as follows : time to occurrence of the adverse event, indication of triggering medication, dose per single administration of suspected drug, strategy for managing suspected drug, details of adverse event (including symptoms), other suspected drugs, concomitant medications, final outcome of adverse event, causality, and basic patient information (age, sex, height, and body weight). The age of the patient was provided as decimal data. Furthermore, because the outcome of the adverse event was classified into five categories, we distinguished death cases from the others for simplicity.

The causality of the adverse event, as determined by the reporting individual, was only available when the outcome was death, so it was not suitable for our analysis. Thus, we selected the following seven items as the demographic data : age, sex, dose, outcome, suspected triggering medication, other suspected drugs, and concomitant medications. The concomitant use of Carbamazepine (CBZ) and valproate (VPA) was checked because CBZ is classified as an aromatic anticonvulsant and is a typical drug with the potential to induce AHS[12], and because VPA increases lamotrigine concentrations slightly more than 2-fold[14].

The occurrence of the AHS triad of fever, skin eruption, and internal organ involvement was also examined. Liver dysfunction is the most frequently involved organ symptom in AHS[15], and, therefore, it was used as a surrogate marker of internal organ involvement. This is because it is hard to discriminate AHS-related reactions from other symptoms.

Ethical issues

This study was approved by the Ethical Committee for Human Research of Akita University. Researchers are required to obtain case-by-case permission prior to using JADER for any study. Therefore, this study was started after permission had been granted.

Results

Demographics

Twenty-two reports of LTG-related DIC were identified in the JADER. The demographic data are listed in Table 1. Median age of the cases was 30, and female cases were dominant in the sex distribution. VPA was prescribed in 59% of the LTG-related DIC cases, where-

Table 1. Demographics

	LTG-related DIC cases (n = 22)
Age (years)†	30 (10-60)
Sex (male/female)	6/16
Other suspected drugs (cases)	6
Death (cases)	4
Concomitant medications	
Valproate (cases)	13
Carbamazepine (cases)	4
Indication	
Epilepsy (cases)	11
Bipolar disorder (cases)	11
Dose of LTG	
25 (mg/single dose)	20
50 (mg/single dose)	1
Blank data	1

LTG : lamotrigine, disseminated intravascular coagulation (DIC), †median (range).

as CBZ was used in 18% of the cases. The indication of LTG was so limited that only two disorders were found and 20 of the 22 cases were administered 25 mg per single dose.

AHS triad

The frequency of occurrence of each symptom is shown in Table 2. In the LTG-related DIC cases, the triad symptoms were observed in 64%, and each of the triad was highly frequently seen (fever, skin eruption, and liver dysfunction were at 91, 100, and 68%, respectively).

Table 2. Triad of anticonvulsant hypersensitivity syndrome (AHS)

	LTG-related DIC cases (n = 22)
Triad of AHS (cases)	14
[Each triad symptom]	
Fever (cases)	20
Skin eruption (cases)	22
Liver dysfunction (cases)	15

LTG : lamotrigine, DIC : disseminated intravascular coagulation.

Discussion

AHS Triad

DIC can occur in the acute course of LTG-induced AHS, as we have previously reported[5,6]. In the current study, we attempted to determine whether LTG-induced DIC was mediated by AHS. The main finding of this study was that the AHS triad could observed highly frequently in LTG-related DIC cases (Table 2). It is plausible that the LTG-induced DIC was strongly related to AHS in this study sample. LTG may have a particular mechanism that induces DIC through a hypersensitivity reaction. More attention should be focused on the risk of DIC and AHS during the use of LTG.

Demographics

We also observed that the doses were quite homogeneous in the LTG group, as shown in Table 1. In almost all cases, the LTG doses remained at their starting levels throughout treatment. The onset of DIC in the LTG group was estimated as acute or subacute. In the two cases in the LTG group that we had previously reported to JADER, early signs of AHS appeared on day 7 or 10 after the first administration of the agent and DIC was diagnosed 4 days after the appearance of AHS in each case[5,6]. These results may also support our research hypothesis that LTG-related DIC is induced by a hypersensitivity reaction to LTG.

Clinical significance and management

The results of this study also indicated that the clinical management of DIC after LTG use is critical. The following main observations were made. First, the number of accumulated cases in the JADER was not insignificant. Similar to our previous experience with the two reported cases, other physicians could encounter such cases, especially in general hospitals. Second, LTG-related DIC tended to emerge acutely or subacutely as described above. Third, DIC may be attributed to LTG hypersensitivity and LTG should be discontinued as soon as possible when hypersensitivity and DIC are observed concurrently. Consequently, the clinical features of DIC after LTG use and its management should be mentioned in the package insert of the drug.

VPA is a best-known agent in LTG use from the viewpoint of drug interaction[16]. In this study, it should be marked that concomitant use of VPA was found in 59 percent of LTG-related DIC cases. VPA might have a clinical potential to induce DIC via the AHS or relevant drug-hypersensitivity phenomenon when used with LTG.

Differences are evident from the information in the package inserts of LTG products between Japan and other countries. GlaxoSmithKline K.K. did not include the potential risk of DIC in the package insert of LTG in Japan, whereas it is mentioned in the product insert documents in the U.K. In the U.S., the risk was previously described in product insert documents, but was omitted in 2010[16]. We believe that the absence of this product warning in Japan endangers Japanese patients and must be improved.

Study strengths and weaknesses

The strengths of this study were the large database size and representativeness of the study subjects. The large database size was made possible by using the JADER. JADER is one of the national medical databases in Japan and can be used by the general public to conduct studies after submission of a simple petition. The representativeness of the study sample with respect to the safety information of drugs is ensured by the reporting system and by domestic law. Any unlisted adverse event in package inserts must be reported to the public organization managing JADER in Japan. Therefore, the 22 cases in the LTG group, where DIC was diagnosed with respect to LTG use from 2008 to 2016, were considered representative of the Japanese population.

This study had a few limitations. Firstly, this study was conducted with indirect data sampling using the JADER. For example, we were unable to identify the actual age, laboratory data, or causalities determined by the individuals reporting the adverse events. For the same reason, we could not confirm each diagnosis of DIC based on each laboratory data in this study. Although the study data was collected indirectly by using the JADER, each data was real and considered as reliable. As we previously reported[5,6], we have experience with two cases of AHS-mediated DIC after LTG use. In both cases, the diagnoses of AHS were reached because of careful differential diagnoses and causations between AHS and LTG use were positive. Secondly, it should be also mentioned that diagnosis of AHS in each reported case might be heterogeneous. AHS is a clinical syndrome, and patient with AHS may or may not Drug-induced hypersensitivity syndrome (DIHS), or other relevant syndromes. The authors could not identify each phenomenon due to the methodological limitation in this study.

Conclusions

The results of this study suggested that a distinct etiology, namely AHS or a phenomenon related to the syndrome, is the underlying mechanism of LTG-related DIC. LTG may induce DIC via AHS. More importance should be placed on the risk of DIC with LTG use and adequate and precise information about this risk should be provided for users in Japan.

Acknowledgments

None

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding

This study received no financial support.

References

1) Brodie, M.J. (1992) Lamotrigine. *Lancet,* **339**, 1397-1400.
2) Schaub, J.E., Williamson, P.J., Barnes, E.W. and Trewby, P.N. (1994) Multisystem adverse reaction to lamotrigine. *Lancet*, **344**, 481.
3) Chattergoon, D.S., McGuigan, M.A., Koren, G., Hwang, P. and Ito, S. (1997) Multiorgan dysfunction and disseminated intravascular coagulation in children receiving lamotrigine and valproic acid. *Neurology*, **49**, 1442-1444.

4) Sauvé, G., Bresson-Hadni, S., Prost, P., Le Calvez, S., Becker, M.C., Galmiche, J., Carbillet, J.P. and Miguet, J.P. (2000) Acute hepatitis after lamotrigine administration. *Dig. Dis. Sci.*, **45**, 1874-1877.
5) Takeshima, M., Ishikawa, H., Shimizu, T., Toyoshima, A. and Manabe, M. (2016) Lamotrigine-induced disseminated intravascular coagulation with anticonvulsant hypersensitivity syndrome : A case report. *Psychosomatics*, **57**, 540-542.
6) Takeshima, M., Ishikawa, H. and Shimizu, T. (2017) Acute respiratory distress syndrome and lamotrigine : A case report. *Psychosomatics*, **58**, 313-316.
7) Schlienger, R.G., Knowles, S.R. and Shear, N.H. (1998) Lamotrigine-associated anticonvulsant hypersensitivity syndrome. *Neurology*, **51**, 1172-1175.
8) Mackay, F.J., Wilton, L.V., Pearce, G.L., Freemantle, S.N. and Mann, R.D. (1997) Safety of long-term lamotrigine in epilepsy. *Epilepsia*, **38**, 881-886.
9) Wong, I.C., Mawer, G.E. and Sander, J.W. (2001) Adverse event monitoring in lamotrigine patients : a pharmacoepidemiologic study in the United Kingdom. *Epilepsia*, **42**, 237-244.
10) Yuen, A.W. and Bihari, D.J. (1992) Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet,* **340**, 618.
11) Knowles, S.R., Shapiro, L.E. and Shear, N.H. (1999) Anticonvulsant hypersensitivity syndrome : incidence, prevention and management. *Drug Saf.*, **21**, 489-501.
12) Mansur, A.T., Pekcan Yaşar, S. and Göktay, F. (2008) Anticonvulsant hypersensitivity syndrome : clinical and laboratory features. *Int. J. Dermatol.*, **47**, 1184-1189.
13) Knowles, S.R., Dewhurst, N. and Shear, N.H. (2012) Anticonvulsant hypersensitivity syndrome : an update. *Expert Opin. Drug Saf.*, **11**, 767-778.
14) Hosoya, R., Uesawa, Y., Ishii-Nozawa, R. and Kagaya, H. (2017) Analysis of factors associated with hiccups based on the Japanese Adverse Drug Event Report database. *PLoS One*, **12**, e0172057.
15) Shear, N.H. and Spielberg, S.P. (1988) Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. *J. Clin. Invest.*, **82**, 1826-1832.
16) GlaxoSmithKline. "Lamictal Full Prescribing Information. (Revised May 2016)" <https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF.>, cited 9 May, 2017.