Case Report
Drug-induced encephalopathy with seizures: a series of case reports

Peisen Qiu, Zhongxin Xu, Lei Xu, Jing Mang, Jinting He, Xiaoyan Li

Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, China
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Abstract: Drug-induced disease is a major clinical disorder; however, neurological manifestations are not common. Madopar, lidocaine, and cephalosporin antibiotics are used commonly in clinical practice. Although encephalopathy resulting from these drugs is rare, it is important to be alert about the serious adverse effects of these common drugs to avoid delay in diagnosis and treatment. Here, we have reported three cases: all were elderly female patients with history of allergy. The patients complained of convulsions and disturbances in consciousness, and were diagnosed with drug-induced encephalopathy, which was relieved by therapy. For elderly people with drug allergies, especially those with abnormal renal function, doctors should pay extra attention to the possibility of drug-induced encephalopathy following the appearance of sudden unconsciousness and seizures. For patients taking long-term oral metoprolol, regular routine blood examination is necessary.

Keywords: Encephalopathy, drug, allergy, seizure

Introduction
The definition of drug-induced encephalopathy remains controversial. Documented by clinicians, brain dysfunction such as convulsions, cognitive dysfunction, abnormal mental behavior, and disturbance of consciousness may occur after medication. Several drugs are reported to induce encephalopathies, including antibiotics, antiviral agents, antidepressants, analgesics, and anesthetics [1]. Similar to other drug-induced diseases, such symptoms will be alleviated or even disappear immediately after stopping the use of relevant inducers, because the disease essentially results from the disturbance of cerebral metabolism rather than structural lesions. Hence, the diagnosis of drug-induced encephalopathy should be made after the exclusion of other possibilities. In the early 1960s, encephalopathy was observed after an overdose of isoniazid, although seizure and unconsciousness were rare toxic effects. In 1977, the Boston Collaborative Drug Surveillance Program reported 26 cases of drug-induced convulsions in 32,812 patients (0.08%).

The diagnosis of drug-induced encephalopathy contains various aspects. First, disorders of cerebral function as seizures or disturbances of consciousness occur suddenly. Subsequently, relevant clinical routine tests for natremia, blood ammonia, or glycemia should be performed to determine the cause of encephalopathy and to exclude the possibilities of hypoglycemia, hepatic encephalopathy, or other diseases. After diagnosis, a therapeutic strategy should be formed. Second, electrophysiological studies and imaging examination should be considered. The main features of drug-induced encephalopathy in EEG are diffuse, and the waveform is unusually mild to violent. Sometimes triphasic waves with intermittent frontal delta activity can be seen. Focal or generalized spike-wave complexes, or generalized and focal slow waves may also be observed. Encephalopathy with general slow and epileptic waves may last for days, weeks, or even several months after the drug is discontinued. Imaging examinations are often comprised of cranial computer tomography (CT) and magnetic resonance imaging (MRI). The results may present as bilateral symmetric high signal intensity lesions in the cerebellar dentate nucleus, midbrain, dorsal pons, medulla, and splenium of the corpus callosum in T2-weighted images of metronidazole-induced encephalopathy. With
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the exception of the corpus callosum, all lesions were irreversible, even if the medication was discontinued. Diffuse cortical and subcortical white matter lesions in symmetric bilateral distribution, mainly including the occipital areas, the cerebellum, and the focal areas of bilateral thalami can be seen in MRI of patients with dexamethasone encephalopathy, but are not clear in T1-weighted imaging characteristic of PRES. Cerebral atrophy can also be observed in valproic acid-induced encephalopathy, especially in the chronic type [1].

Once the primary signs of encephalopathy appear, immediate discontinuation of the suspected drugs can lead to complete reversal of symptoms. The prognosis of drug-induced encephalopathy may be excellent if treated early; moreover, it can sometimes be prevented by adjusting the dosage and monitoring the effective concentrations of the relevant drugs in serum. Intravenous carnitine has been proven to be helpful for the treatment of hyperammonemic encephalopathy, as is the treatment of hemodialysis in valproate-induced encephalopathy. Moreover, short-term hemodialysis often has beneficial effects in the treatment of cefepime-induced encephalopathy [1].

The most common drugs involved were penicillin, hypoglycemic agents, lidocaine, methylxanthines, and antipsychotics [2, 3]. The underlying disease etiology is not fully understood; however, researchers have revealed several mechanisms, including drug neurotoxicity, electrolytic disturbance, hyperammonemia, cerebral receptor dysfunction, encephalopathy, and posterior reversible leukoencephalopathy syndrome (PRES). Here, we have presented three cases of seizure in drug-induced encephalopathy caused by commonly prescribed drugs.

Informed Consent: All patients provided informed consent for publication of their cases.

**Case reports**

**Case 1**

A 78-year-old woman was admitted to our hospital with sudden unconsciousness accompanied by a convulsive attack for 4 h, as indicated by her family. Upon admission, her consciousness was vague, bilateral pupils were equal, both light reflexes were present, and bilateral pathological signs were not prolonged. The patient was uncooperative for the rest of the tests of the nervous system.

Three days before admission to our hospital, owing to fever and cough, the patient was diagnosed with pneumonia in the local hospital and treated with ceftazidime (in a dosage of 2.0 g bid). At 4 h after the application of ceftazidime, convulsive symptoms, along with unconsciousness, appeared. The patient then showed no response to speech, and paroxysmal limb spasms. Urinary incontinence also occurred.

The patient had suffered from hypertension for several years and heart failure for 1 month. She had had renal failure for 5-6 years, with renal anemia, which required the long-term intramuscular administration of erythropoietin every other day. Rectal cancer surgery was performed 40 years previously, where she experienced bilateral pleural effusion for 2 months, and drainage with tubes. Three years ago, after cefepime therapy, consciousness disorders appeared, but the symptoms disappeared after hospitalization.

After admission to our hospital, a chest CT scan showed bilateral pleural effusion. Color Doppler echocardiography presented segmental motion abnormality of the ventricular wall. Serum urea nitrogen was 24.41 mmol/L and creatinine in serum was 405 µmol/L. The cranial MRI showed multiple lacunar infarction lesions in the bilateral fronto-parietal-temporal lobes (Figure 1A-C) with no abnormal signals in DWI (Figure 1D). The 24-h EEG showed extensive sharp waves in the bilateral fronto-parietal-temporal lobes (Figure 2). On the second day of our treatment, the convulsive symptoms disappeared without fever. On the fourth day after treatment, the patient’s consciousness was improved and she could communicate with her family members. A reexamination of the EEG was conducted, which showed generally normal waves (Figure 3).

While analyzing this case, we were aware that the patient exhibited sudden seizures along with disturbance of consciousness, which did not exclude the possibility of encephalitis. When further examination of a lumbar puncture was suggested, her family members refused. We believe that the absence of fever or other symptoms may be the reason why the family...
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The patient refused further examinations. It was considered that the possibility of encephalitis was not high. Ion balance disorder was present in the patient, but clear ion abnormalities were not observed, which was unlikely to be the cause of the convulsive seizure. Cerebrovascular disease, brain trauma, and brain tumor diseases were excluded based on the head MRI examination. Considering the presence of renal dysfunction in the patient, we did not exclude the possibility of renal encephalopathy caused by abnormal renal function. However, the creatinine level in the serum of the patient was not extremely high. Therefore, the possibility of this disease was low. In conclusion, because of the application of intravenous ceftazidime (at a dosage of 2.0 g bid), and in light of the abnormal kidney function, the usage of cefepime treatment that resulted in consciousness disorder 3 years previously, and because the patient was an elderly woman, we suspected with high certainty that the appearance of drug encephalopathy led to seizures and unconsciousness. The patient was diagnosed with drug-induced encephalopathy. At the follow-up by telephone call after 2 weeks, it was stated that the patient had no convulsions and could continue with daily life.

Case 2

A 76-year-old woman had paroxysmal convulsions 5 h before admission to our hospital, accompanied by loss of consciousness, eye rolling, closed teeth, rigid limbs, urinary incontinence, and blurred vision. Pain was relieved approximately 4-5 minutes after the onset of the above symptoms, with intermittent abdominal pain, mainly in the upper abdomen. She was then admitted to the Department of Neurology of our hospital because of convulsions. On admission, she showed pale eyelid conjunctiva, yellowish skin and mucosa, clear consciousness, and slightly slow reactions. Her limb muscle strength was recorded at level 4, her limb muscle tension increased, and bilateral Babinski signs were positive.

The patient had had Parkinson’s disease for more than 10 years, and was orally administered Madopar (one tablet four times per day). She was allergic to penicillin and erythromycin. She had suffered fractures of the femoral head 6 years ago, which were treated surgically. She stated she did not have relevant family medical history.

The cranial CT scan, performed at our hospital, showed demyelination of white matter (Figure 4). Abdominal CT scan showed increased density of the cyst in the right lobe of the liver and gallbladder cavity, bile accumulation, sediment-like stones, complex cyst in the left kidney, and a small amount of pelvic effusion were considered. After admission, routine laboratory examinations were carried out: RBC, 0.57×10^{12}/L; hemoglobin, 57.0 g/L (Figure 5A); BUN, 27.37 mmol/L; and CREA, 424.98 µmol/L. Some laboratory parameters could not be obtained because of hemolysis.

![Figure 1. Cranial MRI of the patient in case 1. A. T1-weighted image showed no other specific signals except lacunar-infarction-like signals. B. T2-weighted image also showed no specific signals. C. T2-FLAIR image presented bilateral symmetric high signal intensity lesions by lateral ventricle. D. DWI image showed no special signals.](image)
The patient presented with hematuria and general pain after hospitalization, which was considered likely to result from hemolysis. Infectious hemolytic anemia was not considered owing to the absence of fever in the patient. As the patient had been taking Madopar orally for a long time and had no recent experience of taking other drugs, it was strongly suspected that Madopar was the cause of drug-induced hemolytic anemia and the subsequent seizure. Then patient was then treated with methylprednisolone and human immunoglobulin. Hematuria disappeared after 2 days, whereas jaundice was aggravated. On the third day of the treatment, icterus was alleviated slightly, whereas the degree of weakness and pain increased, and hemoglobin continued to decrease to 32 g/L (Figure 5B). On the fourth day, icterus in the patient decreased, the general condition of weakness improved slightly, but pain was not alleviated, and HB was 36 g/L (Figure 5C). Subsequently, she was discharged at her family’s request. After discharge, the patient’s family members sent her to a Chinese medicine hospital. After 10 days of treatment in the hospital, the follow-up telephone call revealed that the patient showed no longer had icterus, could eat on her own, and could walk

**Figure 2.** The first EEG examination of the patient in case 1. The result presented extensive sharp waves in the bilateral fronto-parietal-temporal lobes.
without help. The symptoms of static tremor were not obvious, and HB had increased to 56 g/L.

Case 3

The third patient was a 69-year-old woman. Her main complaint was “left limb dysfunction for 2 days with convulsion for 1 day”. She was admitted to a local hospital 2 days before admission to our hospital because of cervical spondylosis. In the hospital, she was treated with steroid injection under local anesthesia with lidocaine. After operation, she could not move her left limb for 5 h until the symptoms were relieved. She could easily raise her left hand and left lower limb. Weakness, limb tremor, and unconscious disorder were also recounted by her. One day prior to admission, paroxysmal

Figure 3. The second EEG examination on the fourth day after treatment. The image showed no obvious abnormal waves.

Figure 4. The cranial CT scan on admission of the patient in case 2. The four images presented different levels of the brain of the patient. They showed demyelination of white matter.
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Convulsions occurred twice, each lasting 10 min. The associated symptoms included tight eyelids, binocular vision, clonic seizures of the limbs, disturbance of consciousness, and foaming in the mouth. The symptoms were relieved by the intravenous injection of a tranquilizer. For further diagnosis and treatment of the disease, she was admitted to our hospital.

The patient had allergies to cephalosporin, penicillin, and other drugs. She had dyspnea, and had undergone appendicitis surgery and ovari-
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an cyst surgery when she was younger. Her family claimed that there was no relevant family medical history.

The patient was examined and the following were identified: occasionally blurred consciousness, clear speech, poor left and right discrimination, finger agnosia, left muscle strength level IV, and postural tremor. Bilateral pathological signs were not observed, the remaining nervous system was not significantly positive. No obvious abnormalities were found in the EEG (Figure 6) and cranial MRI (Figure 7). Laboratory examination showed that WBC was 15.07×10^9/L and the NEUT percentage was 76.0% in the whole blood cell count. In a patient with acute onset, no history of infection, and no abnormal signals in cranial MRI, we can exclude the possibility of cerebrovascular disease and infectious encephalopathy. Given the application of lidocaine in local anesthesia followed by the corresponding clinical symptoms, and after elimination of the possibilities of cerebrovascular disease and encephalitis, we ultimately suspected drug-induced encephalopathy caused by lidocaine that resulted in these symptoms.

Figure 6. EEG examination of the patient in case 3. No obvious abnormal waves were found.

Figure 7. Cranial MRI of the patient in case 3. A. DWI image. B. T2-FLAIR image. The two MRI images showed no abnormal signals.
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Under our treatment, the patient had no convulsions or limb movement disorders 5 days after admission. She was discharged from hospital with clear language, good memory, no postural tremor, and negative bilateral pathological signs.

Discussion

The drug-induced encephalopathy in the first patient was caused by ceftazidime. A third-generation cephalosporin, ceftazidime, has similar safety to most cephalosporins, and has not been reported to affect prothrombin or induce a disulfiram reaction observed with moxalactam and cefoperazone. It is eliminated by the kidney. The half-life of ceftazidime (1.8 h) is similar to that of cefotizoxime (1.3-1.8 h), cefoperazone (1.6-2.1 h), and moxalactam (2.0 h). Apart from the similarity, ceftazidime has unique effects on Pseudomonas aeruginosa compared with other third-generation cephalosporins [4]. In addition, ceftazidime may produce, in addition to common adverse drug reactions, some rare adverse effects such as occupational asthma [5] and neurological reactions [6]. The neurological reactions induced by ceftazidime include encephalitic signs, such as confused state, disturbed vigilance, seizures, and visual and auditory hallucinations, whereas the frequency of seizures and visual and auditory hallucinations was lower than that of other encephalitic symptoms. The precipitating factors include renal failure, underlying brain abnormalities (lacunar infarction, pituitary tumor, stroke, brain metastases, and encephalopathy) and CNS infection. Among these basic status, renal failure occurred in 81.5% of patients, and the dosage of ceftazidime is not usually adjusted to renal function [6]. However, the convolution and disturbance of consciousness induced by ceftazidime has not been reported.

Case 2 was considered to be Madopar-induced hemolytic anemia with secondary epilepsy. It has been reported that therapy with levodopa in combination with carbidopa may cause a skin rash, although the etiology is not yet determined [7]. In addition, serotonin syndrome (SS) has been described in patients who received linezolid in combination with carbidopa-levodopa [8]. Coincidently, levodopa was reported to cause hemolytic anemia [9]. Madopar, the main drug alleviating the motor system symptoms of Parkinson’s disease, may cause some common adverse drug reactions such as nausea, drowsiness, and orthostatic hypotension [10], whereas reactions that start with convolution and hemolytic anemia have not been reported before. A limitation of this case report is the lack of EEG examination and brain MRI. As the patient’s convulsions stopped after she was admitted to the hospital, and the general level of pain in the whole body was very poor, she was a high-risk patient and was not in a suitable condition to undergo EEG and MRI.

Case 3 was associated with lidocaine, which is used widely in clinical work. The case of a 10-year-old girl who was scheduled to receive an elective tenectomy has been reported: a few seconds after fentanyl and lidocaine administration for anesthesia induction, she developed generalized tonic-clonic seizures [11]. However, her final prognosis was good. Another report describes the case of a 5-month-old infant who experienced seizures after receiving viscous lidocaine [12]. To the best of our knowledge, this case is the fifth case of epilepsy caused by lidocaine. It has been reported that 92% of drug-induced convulsions have no neurological sequelae [13].

The prognosis of the three patients was good, which may be related to early identification, discontinuation of relevant drugs, and active treatment. Drug-induced encephalopathy occurs rarely in clinical settings, but still requires clinicians’ vigilance.

In summary, the following can be learned from these three cases: 1. All patients complained of epilepsy onset and were elderly women with a history of drug allergy and presented with epileptic seizures caused by drugs. 2. The onset of the disease was urgent and severe, and the prognosis was better after active treatment. This shows that the prognosis of patients with drug-induced encephalopathy is good. 3. For patients with a history of allergy, attention should be given to the possibility of adverse drug reactions caused by other drugs. It is suggested that after the long-term oral administration of Madopar and other drugs, patients with Parkinson’s disease should regularly check routine blood work to avoid anemia. In elderly patients, lung infection can occur easily; in the application of antibiotics, attention should be paid to the reduction of the creatinine clear-
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We speculate that there are two mechanisms for drug-induced encephalopathy. The first is the immunological theory: there may be special antibodies in patients with allergies, and immune reactions may appear after the application of other drugs, leading to the disturbance of consciousness and seizures. The second is related to the theory of genetics: some people have specific genetic abnormalities and experience adverse drug reactions following the administration of certain drugs.

Conclusion

In elderly people with a history of drug allergies, especially in patients with abnormal renal function, the appearance of sudden unconsciousness and seizures should be considered an indication of drug-induced encephalopathy. Therefore, the use of drugs over time should be considered as a possible cause of encephalopathy. For the patients with Parkinson's disease who are taking long-term oral Madopar, regular review of routine blood tests is necessary to avoid hemolytic anemia.

Disclosure of conflict of interest

None.

Abbreviations

RBC, red blood cell; WBC, white blood cell; HB, hemoglobin; NEUT, Neutrophils; BUN, serum urea nitrogen; CREA, creatinine; EEG, electroencephalogram; CT, Computed Tomography; MRI, magnetic resonance scanning; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NEUT#, absolute value of neutrophil; LYM#, absolute value of lymphocyte; MONO#, absolute value of monocyte; EOS#, absolute value of eosinophil; BASO#, absolute value of basophil.

Address correspondence to: Zhongxin Xu and Lei Xu, Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, China. Tel: +86-13614319995; E-mail: xuzhongxin@jlu.edu.cn (ZXX); Tel: +86-18186818612; E-mail: xuleijlu@jlu.edu.cn (LX)

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