

# Electroencephalographic periodic discharges in Metronidazole-induced encephalopathy: a case report

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## Abstract

**Purpose:** Metronidazole induced encephalopathy (MIE) is a rare disorder of consciousness. The electroencephalographic (EEG) features of MIE have seldom been described.

**Case Report:** A 58-year-old woman had progressive consciousness disturbance during the treatment course of pseudomembranous colitis. She had been placed on metronidazole 500mg three times a day for 52 days. Image studies of brain disclosed lesions over bilateral dentate nuclei of the cerebellum, midbrain and dorsal pons, medulla, periventricular white matter, anterior and posterior splenium. EEG revealed generalized periodic discharges with diffuse background slowing. MIE was considered and metronidazole was discontinued. Two weeks later, the patient had clinic-electrical improvement with normalization of EEG and symptoms.

**Conclusion:** EEG patterns of MIE ranges from diffuse slow waves to generalized periodic discharges. More studies are needed to understand the development of different EEG features and MIE.

**Key Words:** metronidazole induced encephalopathy, generalized periodic discharges

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## INTRODUCTION

Metronidazole-induced encephalopathy (MIE) is an uncommon but critical condition that clinician might encounter, especially during the treatment course of a variety of infectious diseases. Radiological findings revealed consistent lesions over the cerebellar dentate nuclei, midbrain, dorsal pons, medulla, and splenium of the corpus callosum. However, there was rare report of electroencephalographic (EEG) results in MIE. Herein we report a case of MIE with the series change of EEG

patterns and discussed the potential implications of the EEG in guiding the clinical evaluation of MIE.

## CASE PRESENTATION

This 58-year-old lady has history of cervical cancer with hysterectomy and radiation therapy at age 50, which was complicated with radiation cystitis and vesico-vaginal fistula. Six weeks prior to admission, she had painful right hip which was later proved to be attributed to a focal abscess via computed tomography

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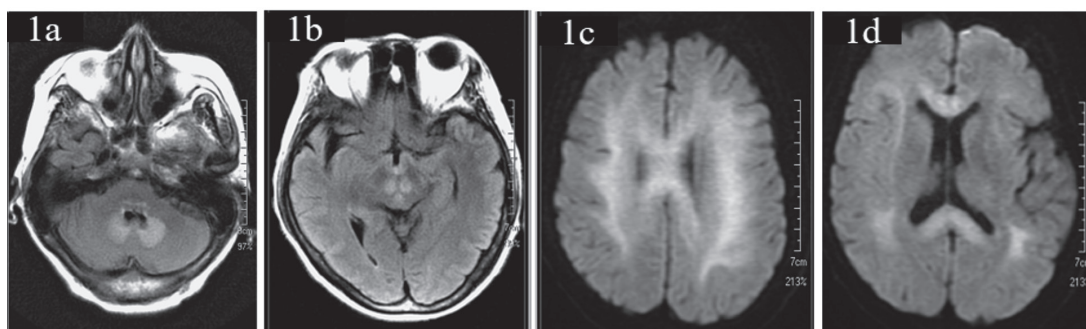
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(CT). She received drainage and antibiotic treatment immediately. She was transferred to our hospital later due to persistent symptoms. Resective arthroplasty was performed for the septic arthritis. However, persistent diarrhea developed and metronidazole was initiated for suspected pseudomembranous colitis since the 6th week after admission, with enteral dose of 500mg three times a day. At the 13th-14th week of hospitalization, rapidly progressive consciousness disturbance developed. She was found stupor, with fine rhythmic movement of both shoulders and head. Physical findings revealed contraction

of upper limbs, and dorsiflexion of plantar responses. Laboratory investigation with electrolytes, liver function tests, renal function tests, and cerebrospinal fluid analysis were within normal range. Serum ammonia was below 17 mcg/dL, C-reactive protein 2.74 mg/dL, procalcitonin 0.09 ng/mL, anti-thyroid peroxidase antibody 119.2 IU/mL, and anti-thyroglobulin 232.5 IU/mL. Magnetic resonance image (MRI) revealed patchy abnormal hyperintensities in fluid attenuation inversion recovery (FLAIR) with restricted diffusion in bilateral periventricular white matter, anterior and posterior splenium of corpus callosum



**Figure 1.** Abnormal high signals in T2 FLAIR at bilateral dentate nuclei of the cerebellum (Fig.1a), midbrain and dorsal pons (Fig.1b) and restricted diffusion in bilateral periventricular white matter (Fig.1c), anterior and posterior splenium of corpus callosum (Fig.1d).



**Figure 2.** Electroencephalography two days after discontinuation of metronidazole

Two days after discontinuation of metronidazole, EEG demonstrated generalized high-voltage sharp wave complexes in quasi-periodic patterns (circles) with triphasic morphology, at intervals of 0.5 second, with maximum over frontal areas.



**Figure 3.** Electroencephalography 13 days after discontinuation of metronidazole

Thirteen days after discontinuation of metronidazole, EEG demonstrated diffuse background slowing, 4-5 Hz, with rare amount of sharp wave complexes (circle). There was an electrical pulp at the F7 lead (arrow).

and without restricted diffusion at bilateral dentate nuclei of the cerebellum, midbrain and dorsal pons and medulla (Fig.1). The above MRI findings were highly suggestive of metronidazole-induced encephalopathy. Metronidazole was discontinued. Two days after discontinuation of the metronidazole, electroencephalogram (EEG) was performed, which revealed generalized high-voltage sharp wave complexes in quasi-periodic patterns with triphasic morphology, at intervals of 0.5 second, with maximum over frontal areas, likely to be quasi-generalized periodic discharges (quasi-GPDs) (Fig.2). Two weeks after discontinuation of metronidazole, she could have occasional eye contact but still remained in bedridden status. She did not have verbal output and could not follow verbal commands. The follow-up EEG was improved with rare amount of periodic discharges (Fig.3). Her infectious condition became under controlled and she was under rehabilitation program. Six months later, she remained vegetative state and EEG disclosed diffusely slow background activity at theta range.

## DISCUSSION

In this report, we describe the case of a patient who presented with typical features of MIE, namely, dysarthria,

unsteady gait, visual disturbance, confusion, and seizure with characteristic neuroimaging findings<sup>(1)</sup>. Her EEG demonstrated GPDs when clinical symptoms were severe, which resolved along with the improvement of clinical symptoms.

Reversibility of image lesions was declared in most studies. However, there were reports of uncertain reversibility or poor prognosis. In the case described by Farmakiotis and Zeluff<sup>(2)</sup>, a 58-year-old man with cryptogenic cirrhosis received metronidazole for *Clostridium difficile* infection with a cumulative dose of over 30 gm. After discontinuation of metronidazole, he never regained his consciousness despite resolution of cerebellar lesions in the follow-up of MRI and was expired owing to bacteremia. Groothoff et al<sup>(3)</sup>. demonstrated permanent coma in a 38-year-old woman with osteomyelitis after treatment with high dose metronidazole with a cumulative dose more than 120 gm. Considering the discrepancy between clinical presentation and imaging findings, alternative studies such as EEG might be needed for evaluating the prognosis in these patients.

Generalized periodic discharges occur in patients with postanoxic encephalopathy, systemic metabolic derangements, ischemic, infectious, structural brain damage, rare conditions such as subacute sclerosing

**Table 1.** Comparisons of reports of MIE (ranking by cumulative dose of Metronidazole)

No.	Demography, reported year	Disease conditions	Comorbidity	Dose (gm)	EEG pattern	Outcome
1	56m <sup>10</sup> , 2013	<i>C. difficile</i> infection	Coronary artery disease, DM, lung fibrosis post transplant	5	GPDs (clinically NCSE)	Recovery
2	68f <sup>11</sup> , 2016	Diarrhea	Cirrhosis, steatohepatitis, umbilical hernia	10.5	DS in theta-delta rhythm	Recovery
3	76f <sup>12</sup> , 2016	Colitis	End stage renal disease under hemodialysis	10.5	Not mentioned	Recovery
4	83f <sup>9</sup> , 2011	Liver abscess	CBD stone status post choledochojejunostomy	21	Not mentioned	Recovery
5	58m <sup>2</sup> , 2016	<i>C. difficile</i> infection	Cryptogenic cirrhosis	over 31.5	Not mentioned	Death
6	65f <sup>13</sup> , 2015	Cholangitis	Hepatitis B cirrhosis, Child C, type 2 DM	33	DS, focal left F-C slowing, epileptiform sharp waves at left F-C	Death
7	58f**	Pseudomembranous colitis	Cervical cancer, septic arthritis, vesico-vaginal fistula	78	GPDs with TM	Vegetative state
8	38f <sup>3</sup> , 2010	Osteomyelitis	Congenital spinal cord lesion, lung disease	132	Signs of diffuse encephalopathy	Death

\*m = male; f = female; *C. difficile* = *Clostridium difficile*; DM = diabetes mellitus; GPDs = generalized periodic discharged; NCSE = non-convulsive status epilepticus; DS = diffuse slowing; F = frontal; C = central; TM = triphasic morphology. \*\*The case in this report.

panencephalitis, Creutzfeldt-Jakob disease, and NCSE<sup>(4)</sup>. In addition, drug-associated GPDs were also reported, such as Cefepime<sup>(5)</sup>, Baclofen<sup>(6)</sup>, Lithium<sup>(7)</sup>. Selective synaptic failure probably plays a role in the onset of persistent GPDs. In a case-control study<sup>(8)</sup> of 200 critically ill patients, 46.0% with GPDs had seizures overall and 23.5% had status epilepticus. In table.1, the EEG patterns of MIE encompassed diffuse slow waves and GPDs with triphasic morphology. GPDs occur in the case 1 and case 7, with the cumulative dose of 5g and 78g, respectively. The former had good recovery and the latter has poor responsiveness. In the 4 cases with cumulative dose more than 30gm, 3 patients expired and 1 patient became vegetative state. Hence, the EEG patterns seemed not to be related to cumulative dose of metronidazole nor indicative of poor prognosis. More data are needed to investigate potential prognostic markers.

In a systemic review for metronidazole-induced central nervous system toxicity, Kuriyama et al<sup>(9)</sup> demonstrated

21 (33%) had altered mental status and 8 (15%) had seizures among the 64 patients. In 2013, Cantador et al.<sup>(10)</sup> reported a case of nonconvulsive status epilepticus (NCSE) induced by metronidazole. Myoclonic jerks with rapid mental deterioration occurred after intravenous infusion of metronidazole, 500mg/day for 10 days. EEG revealed GPDs, suggesting NCSE. After administration of midazolam with EEG monitoring, there was clinico-electrical improvement. As for our case with stupor, fine rhythmic movement of shoulders and head, NCSE was also possible. In 2016, Onder<sup>(11)</sup> documented the EEG in a case of MRI negative MIE. The 68-year-old woman presented with confusion after taking metronidazole with a cumulative dose of 10.5g, and EEG disclosed diffuse continuous theta-delta rhythm. After discontinuation of metronidazole, her consciousness totally recovered, with normal parieto-occipital alpha rhythm in the EEG. Consistent with this report, our case had improvement clinically and electrographically after discontinuation



of metronidazole. Besides, our case underwent higher exposure of metronidazole with a cumulative dose of 78 gm, which may explain the differences in the MRI findings and clinical symptoms. Table.1 lists the comparison of different cases of MIE with analyses of EEG patterns, cumulative doses, and outcome.

## CONCLUSION

It is warranted to monitor patients treated with metronidazole regarding the duration, cumulative doses, and any change of neurologic symptoms. Once altered mental status or other neurologic deficits occur, substitution for metronidazole should be considered. MRI and EEG, unfortunately, could not completely predict the prognosis of MIE. More evidence is needed to contribute the hypothesis.

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