Metronidazole Induced Encephalopathy with Peripheral Polyneuropathy in Patient with Spinal Cord Injury

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INTRODUCTION

Metronidazole is a commonly used antimicrobial agent used for the treatment of protozoal and bacterial infection. This drug is in its inactive state when administered to a patient, allowing selective targeting. Once in the system the drug is taken up by the target and metabolized into its active form, inhibiting its normal function. The most common side effects of metronidazole include nausea, headaches and the metallic taste in the mouth. In some cases, high doses and/or prolong use may produce several neurologic side effects including peripheral neuropathy, cerebellopathy, encephalopathy and seizure.²³⁵,⁷

Recently, we encountered a case of metronidazole-induced encephalopathy (MIE) with peripheral polyneuropathy (PPN) in patient with spinal cord injury (SCI). MIE with PPN is a very rare occurrence let alone a MIE on a patient with spinal cord injury, which has not been previously documented. Whether the encephalopathy and PPN was induced by metronidazole or some other factor in patient with spinal cord injury, diagnosis at first glance proved to be very difficult. This was because the sure signs (ataxia, gait difficulty, tingling sensation in lower extremity and so on) of the drug’s side effects were not present due to the paraplegia. However, observing this patient carefully, we have noticed something that might serve as detection for MIE with PPN despite paraplegia.

CASE REPORT

A 32-year-old woman injured in a skiing accident a month before her visit, was transferred to our institute from another hospital as a result of her paraplegia. Initial workshop at the other hospital showed bursting fractures of T6, T7, T8 vertebral bodies, hemothorax and multiple rib fractures (Fig. 1). Neurologic examination revealed a motor and sensory impairment of grade A at the T6 level, according to the American Spinal Injury Association (ASIA) scale. She was examined for vaginal discharge at the previous hospital and was diagnosed with erosion and acute inflammation of the cervix. She was then treated with 2 g of metronidazole daily for fifty days because of the vaginal discharge.

One month after the first administration of metronidazole, she complained of a mild tingling sensation on both forearms and all fingers as stocking glove type. The patient denied other symptoms including neck pain and hand weakness. However...
laboratory findings from blood and urine samples did not show any specific abnormalities (Hb: 12.4 g/dL, Protein: 5.7 g/ dL, Albumin: 3.5 g/dL, GOT: 38 IU/L, GPT: 59 IU/L, Na: 142 meq/L, K: 4.3 meq/L, Ca: 9.4 mg/dL, P: 4.9 mg/dL). We examined Tinel and Phalen sign and proceeded to do an electrophysiological study in the upper extremities as well as a cervical spine MRI, checking for Carpal Tunnel Syndrome (CTS), syringomyelia, and other complications that might have risen in the patient with spinal cord injury. However the tests revealed normal finding.

Forty five days after the first treatment of metronidazole she developed mild nausea and vomiting with dizziness. We performed esophagogastroduodenoscopy to check for gastric ulcer, but observed only atrophic gastritis on a pyloric antrum. Fifty days after the first medication of metronidazole, we observed dysarthria and weakness of both hands. But, we did not find pathologic nystagmus and diadochokinesia beside dysmetria of hands. Because of paraplegia, we could not examine whether ataxia exist, or not. Laboratory findings from blood showed no abnormalities (Hb: 12.9 g/dL, WBC count: 7,200 uL ESR: 14 mm/hr, Protein: 5.8 g/dl, Albumin: 3.8 g/dl, GOT: 22 IU/L, GPT: 18 IU/L, Na: 138 meq/L, K: 3.9 meq/L, Ca: 9.1 mg/dL, P: 4.7 mg/dL, Vit. B12: 611 pg/ml[200-950], Folate: 4.34 ng/ml[3-17]). The brain magnetic resonanace image (MRI) with diffusion-weighted image (DWI) was performed to rule out brain lesions. We also performed electrophysiological examinations of upper and lower limbs to find signs of peripheral polyneuropathy, simultaneously. We observed high intensities of superior olivary nuclei, dentate nuclei of cerebellum and splenium of corpus callosum on MRI (Figs. 2 and 3). In addition, the findings of electrophysiological examination revealed that amplitudes (base to peak amplitude) were below normal or absent on sensory nerves of more than 3 limbs, on the other hand, onset latency and velocity of those were normal findings. Also latency, amplitude and conduction velocity of motor nerves were normal, but, conduction velocity of peroneal and tibial nerve were lower limit normal. Because of above results, we considered PPN as axonal loss sensory type in this case (Table 1 and 2).

Before we could suspect that metronidazole was behind the new symptoms, we first had to rule out Wernicke Encephalopathy (WE) because of brain MRI images. MIE and WE have similar histologic findings6; therefore it was necessary to differentiate the two. WE have a triad of symptoms including confusion, ophthalmoplegia and gait ataxia while MIE has dysarthria and gait ataxia. We examined the level of thiamine hydrochloride because its deficiency could result in WE. Showing no lack of thiamine hydrochloride, we correlated the MR imaging with the clinical symptoms and diagnosed her as having MIE with PPN and stopped the medication of metronidazole.

Two days later, dysarthria and nausea improved slowly but a little tingling sensation and weakness of both hands persisted for more than three months. Three month later, we rechecked...
Fig. 3. T2-weighted (TR/TE= 4000/115) image (A), FLAIR (TR/TE=8802/161) image (B) and DW (TR/TE=10000/122.2) image (C) demonstrate a focal segmental lesion in the splenium of the corpus callosum (arrows).

Table 1. Motor and sensory nerve conduction study

| Nerve             | Onset Latency (ms) | Peak Latency (ms) | Base to Peak Amplitude (μV) | Conduction Velocity (m/s) |
|-------------------|--------------------|-------------------|-----------------------------|---------------------------|
| Motor nerves      |                    |                   |                             |                           |
| Rt. Median        | 2.9 (≤3.6)         | 8,200 (≥5,000)    | 49 (≥50)                    |                           |
| Rt. Ulnar         | 1.9 (≤4.2)         | 10,000 (≥5,000)   | 53 (≥50)                    |                           |
| Rt. Radial        | 1.4 (≤2.0)         | 6,700 (≥5,000)    | 60 (≥50)                    |                           |
| Lt. Median        | 2.5 (≤3.6)         | 9,300 (≥5,000)    | 48 (≥50)                    |                           |
| Lt. Ulnar         | 1.5 (≤4.2)         | 7,800 (≥5,000)    | 50 (≥50)                    |                           |
| Lt. Radial        | 1.2 (≤2.0)         | 6,100 (≥5,000)    | 51 (≥50)                    |                           |
| Rt. Peroneal      | 3.4 (≤6.0)         | 9,000 (≥2,500)    | 34 (≥40)                    |                           |
| Rt. Tibial        | 3.2 (≤6.0)         | 2,200 (≥5,000)    | 37 (≥40)                    |                           |
| Lt. Peroneal      | 4.0 (≤6.0)         | 8,300 (≥2,500)    | 39 (≥40)                    |                           |
| Lt. Tibial        | 2.4 (≤6.0)         | 2,600 (≥5,000)    | 38 (≥40)                    |                           |
| Sensory nerves    |                    |                   |                             |                           |
| Rt. Median        | 2.1 (≤3.6)         | 2.8               | 10 (≥10)                    | 62 (≥45)                  |
| Rt. Ulnar         | 1.8 (≤3.4)         | 2.5               | 6 (≥10)                     | 58 (≥45)                  |
| Rt. Radial        | 2.0 (≤2.0)         | 2.5               | 8 (≥10)                     | 60 (≥40)                  |
| Lt. Median        | 2.3 (≤3.6)         | 2.9               | 8 (≥10)                     | 61 (≥45)                  |
| Lt. Ulnar         | 1.8 (≤3.4)         | 2.6               | 8 (≥10)                     | 62 (≥45)                  |
| Lt. Radial        | 1.7 (≤2.0)         | 2.4               | 7 (≥10)                     | 56 (≥40)                  |
| Rt. Sural         | Absent (≤3.5)      | Absent            | Absent (≥10)                | - (≥40)                   |
| Lt. Sural         | Absent (≤3.5)      | Absent            | Absent (≥10)                | - (≥40)                   |
| Rt. Superficial peroneal | Absent (≤3.5) | Absent | Absent (≥10) | - (≥40) |
| Lt. Superficial peroneal | Absent (≤3.5) | Absent | Absent (≥10) | - (≥40) |

The numeric values in parentheses refer to normal laboratory values. Rt., right; Lt., left.

the electrophysiological condition in the upper and lower extremity, and it did not revealed-some recovery.

**DISCUSSION**

Neurotoxicity is one of the more serious adverse effects of metronidazole therapy, but it is very rare. The types of neurological side effects ranges from frequent reports of reversible cerebellopathy and peripheral neuropathy, to other uncommon, but documented, neurotoxicities such as encephalopathy, seizure and mental confusion.

Ahmed et al. described the imaging findings of metronidazole toxicity in 1995 in a 45-year-old woman who developed nausea, vomiting, dysarthria and confusion after consuming 35 g of metronidazole over a 30-day course of therapy\(^1\). Horlen et al. reported imaging findings of presumed metronidazole toxicity in a 35-year-old male patient with liver cirrhosis who had consumed greater than 60 g metronidazole over a 55-day period and developed clinical symptoms consistent with metronidazole toxicity in 2000\(^5\). Heaney et al. reported imaging findings of a 74-year-old male patient with progressive bilateral lower extremity weakness and dysarthria in 2003\(^4\). The patient had consumed a total of more than 75 g metronidazole over 8-weeks period.

In each of these cases, including ours, there was a symmetric-
Table 2. Follow up motor and sensory nerve conduction study

| Nerve                      | Onset Latency (ms) | Peak Latency (ms) | Base to Peak Amplitude (µV) | Conduction Velocity (m/s) |
|----------------------------|--------------------|-------------------|-----------------------------|---------------------------|
| Motor nerves               |                    |                   |                             |                          |
| Lt. Median                 | 2.1 (≤3.6)         | 3.0               | 10 (≥10)                    | 61 (≥45)                  |
| Rt. Median                 | 1.9 (≤3.4)         | 2.8               | 12 (≥10)                    | 56 (≥45)                  |
| Rt. Radial                 | 1.6 (≤2.0)         | 2.3               | 11 (≥10)                    | 64 (≥40)                  |
| Lt. Median                 | 2.3 (≤3.6)         | 3.1               | 12 (≥10)                    | 59 (≥45)                  |
| Lt. Radial                 | 1.9 (≤3.4)         | 3.4               | 11 (≥10)                    | 57 (≥45)                  |
| Lt. Ulnar                  | 2.0 (≤2.0)         | 2.7               | 14 (≥10)                    | 66 (≥40)                  |
| Lt. Sural                  | 2.7 (≤3.5)         | 3.8               | 7 (≥10)                     | 42 (≥40)                  |
| Lt. Peroneal               | 2.9 (≤3.5)         | 4.2               | 7 (≥10)                     | 42 (≥40)                  |
| Lt. Superficial peroneal   | 2.5 (≤3.5)         | 3.7               | 11 (≥10)                    | 43 (≥40)                  |
| Lt. Superficial peroneal   | 2.4 (≤3.5)         | 3.9               | 12 (≥10)                    | 43 (≥40)                  |

The numeric values in parentheses refer to normal laboratory values. Rt., right; Lt., left.

MIE and toxic neuropathy can be occurred by neurologic complications of metronidazole. MIE and toxic neuropathy can produce many kinds of neurologic symptoms. In special circumstances such as a paraplegia patient, these symptoms may not be present. However, if a tingling sensation in the hands or one of cerebellar symptoms such as dysarthria, dysmetria, and so on, is observed in patient with spinal cord injury, it is important to consider and to evaluate a possibility of peripheral polyneuropathy, or encephalopathy especially,

**CONCLUSION**

MIE is a reversible disease which can improve a few weeks after discontinuation of metronidazole\(^{1,5,6}\). Therefore, correct and early diagnosis is very important to treat patients with MIE. But considering the rare situation the patient was in, MIE or other neurological problems may be difficult to diagnose, especially when such side effects are not common. The importance of an active differential diagnosis can be seen in our case. Whether the initial tingling of the hands may have been a sign of early MIE or other neurological problem, it would be the best to consider all possible causes before the onset of new symptoms, especially when the severity of the disease is measured by the time of detection.
patient take some metronidazole, because an early detection means a better recovery.

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