e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

METRONIDAZOLE-INDUCED REVERSIBLE CEREBELLAR ATAXIA AND DENTATE NUCLEUS LESIONS: A CASE REPORT

[1]Chun-Yu Liang, [1]Shang-Chang Ho, [2]Wei-Liang Chen, [1,3]Chieh-Sen Chuang

[1]Departments of Neurology, Changhua Christian Hospital, Changhua, Taiwan.
[2]Departments of Medical Imaging, Changhua Christian Hospital, Changhua, Taiwan.
[3]Department of Life Sciences, National Chung-Hsing University, Taiwan.

Corresponding Author:- **Chieh-Sen Chuang**
E-mail: 83954@cch.org.tw

Article Info
Received 15/01/2015
Revised 27/02/2015
Accepted 12/03/2015

Key words:
Cerebellar ataxia, Metronidazole.

ABSTRACT
Cerebellar ataxia is an uncommon side effect of metronidazole. Here, we present a case of cerebellar ataxia and bilateral cerebellar dentate nucleus lesions following the long-term use of metronidazole; these symptoms and imaging findings resolved rapidly after discontinuing use of the drug. A 67 year-old man, who was admitted because of a brain abscess, intravenously received ceftriaxone (2 g) every 12 hours and metronidazole (500 mg) every 6 hours after admission. After 64 days of metronidazole treatment, severe dysarthria, ataxia, down-beat nystagmus in all directions, and distal paresthesia in 4 limbs developed. Brain magnetic resonance imaging (MRI) showed hyperintense lesions over bilateral cerebellar dentate nuclei on T2-weighted, fluid-attenuated inversion-recovery, diffusion-weighted, and apparent diffusion coefficient images, with mild T1 gadolinium contrast enhancement. The patient's cerebellar symptoms completely resolved within 12 days after discontinuing the use of metronidazole. Follow-up MRI 27 days later revealed complete resolution of the aforementioned findings. However, the numbness and tingling sensation over the 4 distal limbs persisted at a 6-week follow-up consultation. Prolonged use of metronidazole can lead to reversible cerebellar ataxia and dentate nucleus lesions, from which total resolution can be expected upon drug discontinuation. When the symptoms of metronidazole toxicity develop, clinicians should discontinue using the drug immediately. Specific MRI findings are suitable tools that facilitate diagnosing metronidazole-induced central nervous system toxicity.

INTRODUCTION

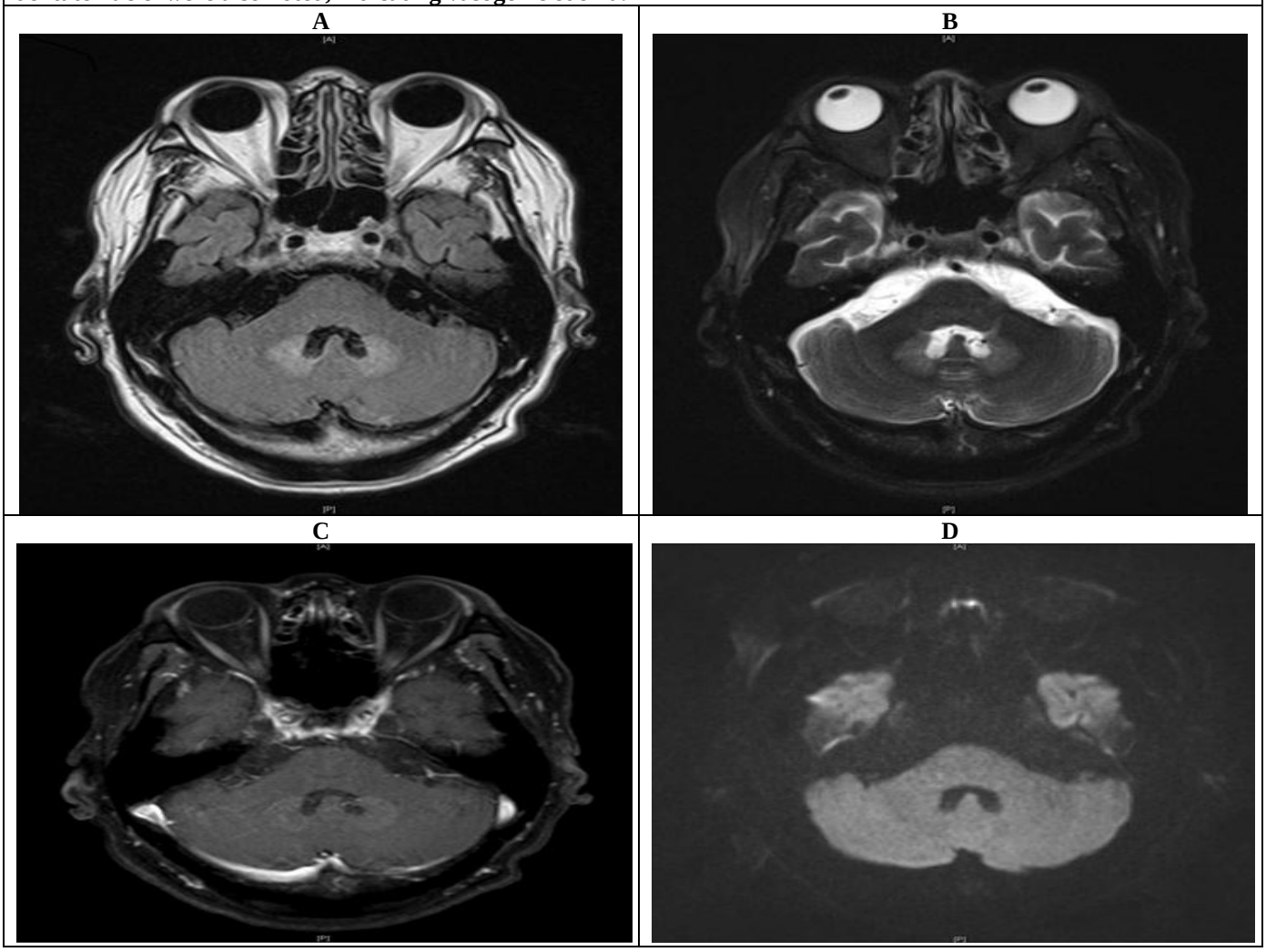
Metronidazole is a nitroimidazole antimicrobial agent that is widely used for treating anaerobic infection, amebiasis, giardiasis, and trichomoniasis, and eradicating *Helicobacter pylori* [1]. The typical side effects are gastrointestinal symptoms including nausea, anorexia, abdominal cramping, diarrhea, and vomiting [2]. Metronidazole is generally used for a short duration of 10–14 days. Long-term use can cause neurotoxicity, including cerebellar ataxia, encephalopathy, seizure disorder, peripheral neuropathy, autonomic neuropathy [3], and optic neuropathy [4]. In this paper, we report a case of brain abscess with cerebellar ataxia and bilateral cerebellar dentate nucleus lesions resulting from the long-term use of metronidazole; these symptoms and imaging findings resolved rapidly after discontinuing use of the drug.

Case report

A 67 year-old man had a medical history of hypertension, hyperlipidemia, and previous lacunar stroke. He was admitted because of a brain abscess. The initial symptoms were fever and mildly slurred speech without obvious focal weakness or sensory impairment. He intravenously received ceftriaxone (2 g) every 12 hours and metronidazole (500 mg) every 6

hours after admission. He retained normal renal and hepatic functions. Progressive dizziness, nausea, an unsteady gait (he experienced a falling accident), severe slurred speech, and distal paresthesia in 4 limbs developed after 64 days of antibiotic treatment. A neurologic examination revealed bilateral finger-nose-finger dysmetria, bilateral heel-knee-shin ataxia, severe dysarthria, down-beat nystagmus in all directions, a rebound phenomenon, pendular knee jerk, and hypoalgesia in a glove and stocking distribution, as well as preserved joint position sense, normal deep tendon reflex, and full muscle power. Brain magnetic resonance imaging (MRI) showed hyperintense lesions over bilateral cerebellar dentate nuclei on T2-weighted images, fluid-attenuated inversion-recovery (FLAIR) images, diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) maps, with mild T1 gadolinium contrast enhancement. (Figure 1). A nerve conduction study revealed decreased amplitudes and normal latencies of the sensory action potentials in the bilateral median, ulnar, and sural nerves as well as relatively normal motor action potentials. Temperature threshold testing showed increased warm and cold thresholds over the thenar eminences and dorsolateral feet, indicating small-fiber neuropathy. According to the aforementioned findings, we suspected metronidazole toxicity. We discontinued the use of metronidazole. Nystagmus disappeared 4 days after discontinuing metronidazole treatment. Twelve days after discontinuing metronidazole, the aforementioned symptoms, except the distal paresthesia in 4 limbs, completely resolved. Follow-up MRI 27 days later revealed complete resolution of the aforementioned findings (Figure 2). However, the numbness and tingling sensation over 4 distal limbs persisted for 6 weeks, and partial recovery was observed after 12 weeks of follow-up.

Figure 1 MRI at the onset of the cerebellar symptoms. T2 FLAIR (A) and T2-weighted (B) images revealed symmetrical hyperintense lesions over bilateral cerebellar dentate nuclei, with mild T1 gadolinium contrast enhancement (C). Slightly high DWI signal intensity (D) and a corresponding high ADC value (E) over bilateral dentate nuclei were also noted, indicating vasogenic edema.



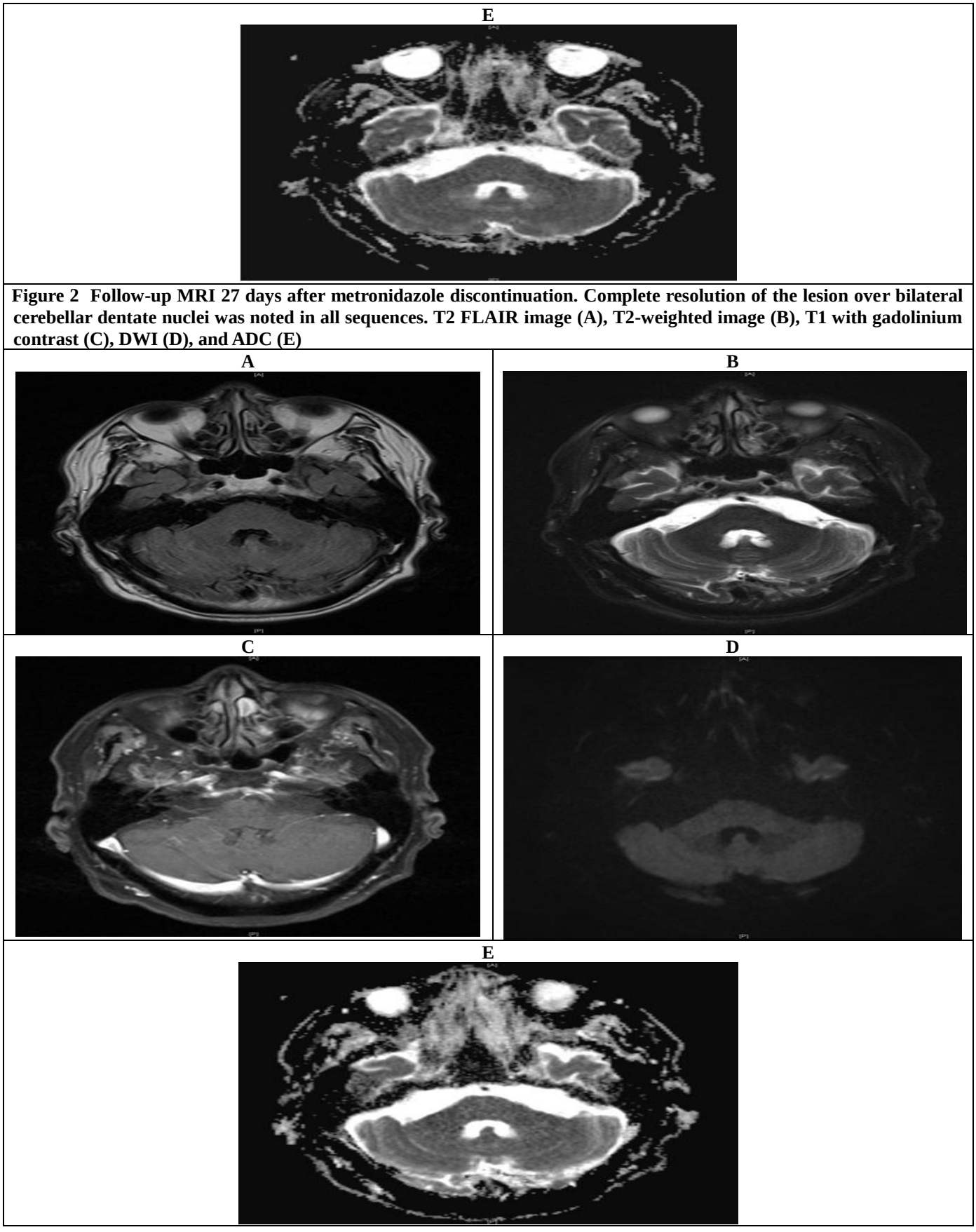


Figure 2 Follow-up MRI 27 days after metronidazole discontinuation. Complete resolution of the lesion over bilateral cerebellar dentate nuclei was noted in all sequences. T2 FLAIR image (A), T2-weighted image (B), T1 with gadolinium contrast (C), DWI (D), and ADC (E)

DISCUSSION

Cerebellar ataxia is not a typical side effect in patients using metronidazole. We described a case of brain abscess accompanied by cerebellar ataxia, dysarthira, down-beat nystagmus, and distal paresthesia in 4 limbs following long-term metronidazole use; these symptoms resolved rapidly after discontinuing the use of the drug, and the lesion over bilateral cerebellar dentate nuclei that was observed using MRI was reversible.

According to previous reports, cerebellar toxicity is related to wide ranges in the total dose (from 25 to 1080 g) [5] and therapeutic duration (from 5–730 days) of metronidazole use [6]. Deenadayalu et al described a 50-year-old a man who developed ataxia and dysarthria after taking a metronidazole dose even lower than that mentioned in previous studies (7.5 g total, 500 mg orally 3 times daily for 5 days) [7]. Both intravenously and orally administering metronidazole at a daily dose averaging 1.6 g can lead to neurologic toxicity; most reported cases were treated by administering metronidazole orally [6]. Our patient received intravenous metronidazole (2 g) daily for 64 days, and the total dose was 126.5 g.

The dentate nucleus is a common target for metronidazole-induced central nervous system (CNS) toxicity. In a previous study, symmetrical hyperintense dentate nucleus lesions were observed on the MRI T2-weighted and FLAIR images of 85% of the patients [8]. Less common locations include the midbrain, corpus callosum (splenium), pons, medulla, cerebral subcortical white matter, and basal ganglia [8,9]. Diffusion-weighted magnetic resonance imaging is used widely in evaluating acute cerebral ischemia [10]. DWI and ADC are considered useful in differentiating between cytotoxic edema and vasogenic edema. A high DWI signal intensity and a reduced ADC value indicate cytotoxic edema, whereas a low, iso, or slightly high DWI signal intensity with a normal or elevated ADC value indicates vasogenic adema [11,12]. The mechanisms of metronidazole-induced neurotoxicity in gray matter and white matter lesions may differ [8]. Previous reports have indicated that vasogenic edema was noted in the cerebellar dentate nuclei, midbrain, pons, and medulla (involving mainly gray matter) [13,14], and cytotoxic edema was noted in the splenium of corpus callosum, subcortical white matter, internal capsule, and anterior commissure (involving white matter) [15]. However, Lee et al. presented a 76-year-old woman who developed bilateral cerebellar dentate nucleus lesions according to MRI using a high DWI signal intensity and a corresponding low ADC value, indicating cytotoxic edema following prolonged use of metronidazole [16]. Our patient exhibited a slightly high DWI signal intensity and a corresponding high ADC value over bilateral cerebellar dendate nuclei, suggesting vasogenic edema. Several previous studies have reported no gadolinium contrast enhancement on T1-weighted images [8,13,17,18]. However, we observed T1 gadolinium contrast enhancement over bilateral cerebellar dentate nuclei in the images of our patient presenting with metronidazole-induced CNS toxicity. We suppose that the MRI findings differed because of differences in the duration of metronidazole use or the severity of neurotoxicity.

Bradley et al asserted that metronidazole can induce sensory axonal degeneration of both myelinated and unmyelinated fibers at all fiber sizes according to pathology [19]. Previous reports have indicated that these patients exhibited decreased amplitudes of sensory action potentials [19,20]. Similar findings were noted in our case. Our patient developed distal paresthesia in 4 limbs and hypoalgesia in a glove and stocking distribution, but his joint position sense and muscle power were preserved after long-term intravenous metronidazole use. The temperature threshold testing of our patient showed increased warm and cold thresholds over the thenar eminences and dorsolateral feet, suggesting that long-term metronidazole use induces small-fiber sensory neuropathy.

Our patient exhibited an improvement in cerebellar symptoms approximately 4 days after metronidazole was discontinued. His cerebellar symptoms were completely resolved within 12 days after drug cessation. Follow-up MRI 27 days later revealed a total resolution of the bilateral cerebellar dentate nucleus lesions. However, distal paresthesia in 4 limbs persisted after several weeks of follow-up. Most relevant published reports have described total recovery of the clinical cerebellar ataxic symptoms and total resolution of the MRI findings after metronidazole use was discontinued in patients with CNS toxicity [5,6,21]. The recovery time for the CNS symptoms ranged from 4 to 120 days, whereas the resolution time for the MRI findings has been extended (1–32 weeks) to achieve a total resolution [6,16]. Paresthesia usually persisted after weeks of follow-up [5], probably because the etiology is axonal degeneration rather than demyelination [19].

In conclusion, prolonged metronidazole use can lead to reversible cerebellar ataxia and dentate nucleus lesions, from which total resolution can be expected upon drug discontinuation. Clinicians must be more attentive toward patients receiving long-term metronidazole therapy. When the symptoms of metronidazole toxicity develop, we should discontinue use of the drug immediately. Specific MRI findings are suitable tools that facilitate diagnosing metronidazole-induced CNS toxicity.

REFERENCES

1. Lofmark S, Edlund C, Nord CE. (2010). Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis*, 50 Suppl 1, S16-23.
2. Nigwekar SU, Casey KJ. (2004). Metronidazole-induced pancreatitis. A case report and review of literature. *JOP*, 5, 516-9.

3. Hobson-Webb LD, Roach ES, Donofrio PD. (2006). Metronidazole: newly recognized cause of autonomic neuropathy. *J Child Neurol*, 21, 429-31.
4. McGrath NM, Kent-Smith B, Sharp DM. (2007). Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol*, 35, 585-6.
5. Patel K, Green-Hopkins I, Lu S, Tunkel AR. (2008). Cerebellar ataxia following prolonged use of metronidazole: case report and literature review. *Int J Infect Dis*, 12, e111-4.
6. Graves TD, Condon M, Loucaidou M, Perry RJ. (2009). Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient. *J Neurol Sci*, 285, 238-40.
7. Deenadayalu VP, Orinion EJ, Chalasani NP, Yoo HY. (2005). Abnormal enhancing lesion of dentate nuclei causing neurologic symptoms induced by metronidazole toxicity. *Clin Gastroenterol Hepatol*, 3, A29.
8. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. (2007). MR imaging of metronidazole-induced encephalopathy: lesion distribution and diffusion-weighted imaging findings. *AJNR Am J Neuroradiol*, 28, 1652-8.
9. Kuriyama A, Jackson JL, Doi A, Kamiya T. (2011). Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol*, 34, 241-7.
10. Beauchamp NJ, Jr., Ulug AM, Passe TJ, van Zijl PC. (1998). MR diffusion imaging in stroke: review and controversies. *Radiographics*, 18, 1269-83; discussion 1283-5.
11. Moritani T, Shrier DA, Numaguchi Y, Takase Y, Takahashi C, Wang HZ, et al. (2000). Diffusion-weighted echo-planar MR imaging: clinical applications and pitfalls - a pictorial essay. *Clin Imaging*, 24, 181-92.
12. Karaarslan E, Arslan A. (2008). Diffusion weighted MR imaging in non-infarct lesions of the brain. *Eur J Radiol*, 65, 402-16.
13. Heaney CJ, Campeau NG, Lindell EP. (2003). MR imaging and diffusion-weighted imaging changes in metronidazole (Flagyl)-induced cerebellar toxicity. *AJNR Am J Neuroradiol*, 24, 1615-7.
14. Kim DW, Park JM, Yoon BW, Baek MJ, Kim JE, Kim S. (2004). Metronidazole-induced encephalopathy. *J Neurol Sci*, 224, 107-11.
15. Seok JI, Yi H, Song YM, Lee WY. (2003) Metronidazole-induced encephalopathy and inferior olivary hypertrophy: lesion analysis with diffusion-weighted imaging and apparent diffusion coefficient maps. *Arch Neurol*, **60,** 1796-800.
16. Lee SS, Cha SH, Lee SY, Song CJ. (2009). Reversible inferior colliculus lesion in metronidazole-induced encephalopathy: magnetic resonance findings on diffusion-weighted and fluid attenuated inversion recovery imaging. *J Comput Assist Tomogr*, 33, 305-8.
17. Bonkowsky JL, Sondrup C, Benedict SL. (2007). Acute reversible cerebellar lesions associated with metronidazole therapy. *Neurology*, 68, 180.
18. Kim H, Kim YW, Kim SR, Park IS, Jo KW. (2011). Metronidazole-induced encephalopathy in a patient with infectious colitis: a case report. *J Med Case Rep*, 5, 63.
19. Bradley WG, Karlsson IJ, Rassol CG. (1977). Metronidazole neuropathy. *Br Med J*, 2, 610-1.
20. Coxon A, Pallis CA. (1976). Metronidazole neuropathy. *J Neurol Neurosurg Psychiatry*, 39, 403-5.
21. Woodruff BK, Wijdicks EF, Marshall WF. (2002). Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med*, 346, 68-9.