

Clinical and Neuroradiological Spectrum of Metronidazole Induced Encephalopathy: Our Experience and the Review of Literature

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ABSTRACT

Metronidazole is an antimicrobial agent mainly used in the treatment of several protozoal and anaerobic infections, additionally, is often used in hepatic encephalopathy and Crohn disease. Apart from peripheral neuropathy, metronidazole can also cause symptoms of central nervous system dysfunction like ataxic gait, dysarthria, seizures, and encephalopathy which may result from both short term and chronic use of this drug and is collectively termed as “metronidazole induced encephalopathy”(MIE). Neuroimaging forms the backbone in clinching the diagnosis of this uncommon entity, especially in cases where there is high index of suspicion of intoxication. Although typical sites of involvement include cerebellum, brain stem and corpus callosum, however, lesions of other sites have also been reported. Once diagnosed, resolution of findings on Magnetic Resonance Imaging (MRI) of the Brain along with clinical improvement remains the mainstay of monitoring. Here we review the key clinical features and MRI findings of MIE as reported in medical literature. We also analyze implication of use of this drug in special situations like hepatic encephalopathy and brain abscess and discuss our experience regarding this entity.

Keywords: Cerebellum, Corpus callosum, Magnetic resonance imaging, Nitroimidazoles, Toxicity

INTRODUCTION

Metronidazole is an antimicrobial agent commonly used in the treatment of several protozoal and anaerobic infections. Its main indications are trichomonal infection, amoebiasis, *Helicobacter Pylori* infection and *Clostridium difficile* associated diarrhea. Additionally, it is often used in Crohn disease and hepatic encephalopathy. Though it is well tolerated in common setting, patient may experience serious neurologic side effects in both long term and short term use. This includes peripheral neuropathy, cerebellar dysfunction, visual impairment, vestibulotoxicity, cochleotoxicity, ataxic gait, dysarthria, seizures and encephalopathy [1-6]. The incidence of metronidazole induced encephalopathy (MIE) is not known [7]. Neuroimaging manifestations of metronidazole toxicity mainly include lesions of the cerebellum, brain stem and corpus callosum [8,9]. If present, characteristic imaging findings and partial or complete normalization of these findings may sometimes be of immense help in clinching the diagnosis of this uncommon entity, especially in cases where there are confounding factors. The first case of MIE was published way back in 1977 [10]. Since then several cases have been reported and awareness of this entity among clinicians have substantially increased especially in the last decade. But still many questions remain unanswered and hence this entity needs further research and clarifications.

EPIDEMIOLOGY

Maximum cases of brain toxicity from metronidazole are reported from United States and Korea, though there have been few case reports worldwide including India, Japan, Australia, Canada, United Kingdom, Belgium, Chile, Germany, Israel, Netherlands, Nigeria, Taiwan, Tunisia, and Turkey. Median duration of development of complications from treatment initiation is 15 days (range 1-90 days) and average cumulative dose is 93.4g (range, 0.25-1095g) [11]. There is no sex predisposition and majority of reports describe adult cases, though there have been a few pediatric cases as well [12].

SIGNS AND SYMPTOMS

Out of the majority of published case reports of metronidazole toxicity to the Central nervous system, maximum cases presented

with cerebellar dysfunction (75%) followed by altered mental status (33%) and seizures (13%) [11]. Among cerebellar dysfunction, dysarthria, ataxia, dysmetria and nystagmus were most common findings on examination in descending order of frequency [11]. Altered mental status is generally a part of the encephalopathy, however, it can be due to non convulsive status as well [13]. Metronidazole toxicity can also present as extrapyramidal manifestations. There are several reported cases of chorea and myoclonus as presenting symptom [14-16]. Researchers have also reported pure sensorineural hearing loss as a presenting symptom [17].

MECHANISMS OF TOXICITY

The mechanism of neurotoxicity induced by metronidazole still remains unclear, though several hypothesis have been proposed by various researchers [3,18-24]. Metronidazole concentration is fairly high in the extracellular space of brain which perhaps contributes to its toxicity [25]. Intermediate metabolites of metronidazole may bind to RNA or DNA of the neuronal cells [3,18]. Metronidazole also induces oxidation of norepinephrine, dopamine and other catecholamine derivatives to form semiquinone and nitro anion radicals which reduce tissue oxygen and generate the superoxide radical increasing water content and causing axonal swelling [19]. Vascular spasms may also produce reversible localized ischemia as seen in cases of “true” diffusion restriction [8]. Double peak of lactate on Magnetic Resonance Spectroscopy (MRS) as reported in some cases point to a mitochondrial insult as a plausible pathogenesis [20,21].

Gamma-amino butyric acid receptor modulation within the cerebellum and vestibular systems has been studied in dogs as a model for metronidazole induced toxicity [22]. Experimental studies have also been performed on which have revealed lesions mainly of brain stem and cerebellum [23-26]. However, pathologic changes in basal ganglia, corpus callosum or white matter have not been observed. Additionally, researchers have also reported similar clinical features including encephalo-neuropathy with other 5-nitroimidazoles like tinidazole [27].

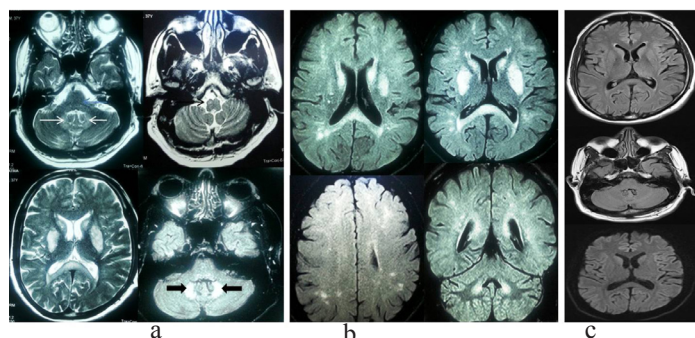
IMAGING

Imaging findings in metronidazole toxicity to the brain are diverse and are of utmost importance for diagnosis. The major sites of

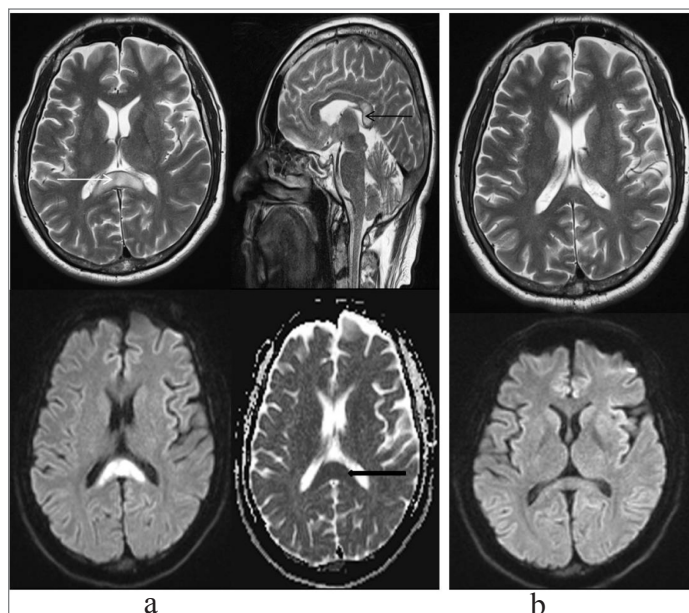
involvement reported in the literature are in form of symmetrical T2W or FLAIR hyperintensities with minimal hypointensity on T1W images in the areas of cerebellar dentate nucleus (most characteristic), midbrain (including periaqueductal region), splenium of the corpus callosum, dorsal pons, medulla, inferior colliculus, subcortical white matter, basal ganglia, thalamus and middle cerebellar peduncles in decreasing order of frequency [28-32] [Table/Fig-1-4]. Diffusion restriction at these sites has been mentioned as a frequent observation but Apparent Diffusion Coefficient (ADC) values have been variable i.e. - low, normal or high [28,30,33]. ADC is actually a measure of the magnitude of diffusion (of water molecules) within tissue, and is commonly clinically calculated using MRI with diffusion weighted imaging (DWI). Diffusion restriction in DWI imaging with high or normal ADC points toward axonal swelling or vasogenic oedema as a pathology but low ADC (cytotoxic oedema) or "true" restriction points towards ischemic process [8]. There is some evidence that there are often low ADC values along with diffusion restriction selectively in the corpus callosum lesions signifying cytotoxic oedema (a pure ischemic process) and a poor outcome [28]. Although, major case studies do not mention contrast enhancement as a feature, recently Furukawa et al., reported multiple contrast-enhancement of lesions in the corpus callosum with cystic degeneration in follow-up imaging, making it difficult to differentiate from the lesions seen in Marchiafava-Bignami disease [34]. Additionally, there are cases showing asymmetric lesions in the subcortical white matter, thus not following the pattern of metabolic or drug induced encephalopathy in which generally symmetric lesions are seen [33] [Table/Fig-1]. There are a few case reports which mention double lactate peak in MRS similar to that seen in mitochondrial pathology [20,21]. We recently encountered a young male patient presenting with episodic dysarthria and peripheral neuropathy who was on metronidazole for chronic bowel dysfunction. There was evidence of involvement of both genu and body of corpus callosum in this patient which has been not been reported earlier in isolation, although involvement of splenium of corpus callosum is a relatively frequently identified finding in this clinical entity [Table/Fig-3].

DIFFERENTIALS

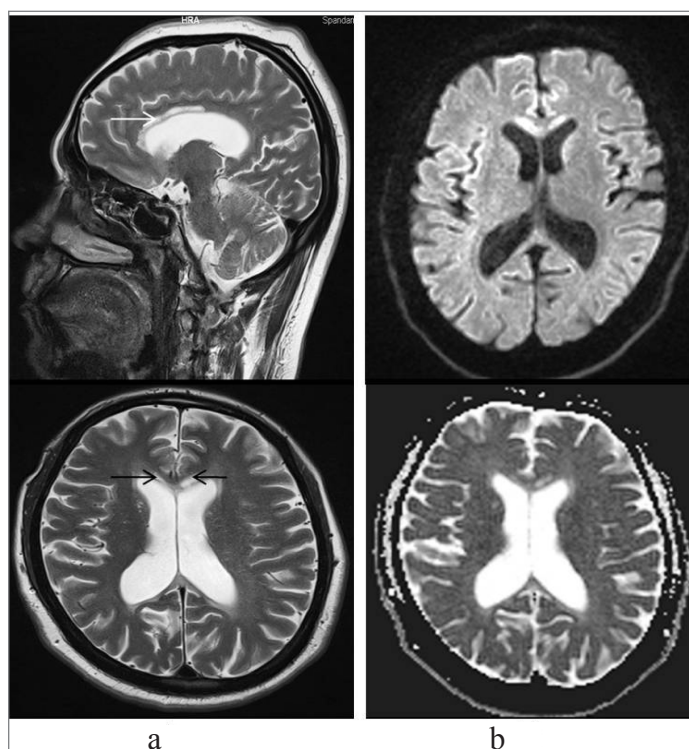
Other acute encephalopathies where there may be bilateral T2 hyperintensities of the dentate nuclei are methyl bromide intoxication [35], enteroviral encephalomyelitis [36] and maple syrup urine disease [37]. T2 hyperintense lesions of the splenium may be observed in various demyelinating disorders (Marchiafava-Bignami disease, osmotic myelinolysis etc.) and these lesions may be transiently seen in disorders like epilepsy (overdose or abrupt withdrawal), acute infectious encephalitis, demyelinating lesions including acute disseminated encephalomyelitis or



[Table/Fig-1]: A 43-year-old man developed gait ataxia & incoherent talk after 6 days of metronidazole therapy for amoebic dysentery. (a) T2W MRI shows hyperintensities in bilateral dentate nuclei (white thin arrows), inferior olive (black thin arrow), bilateral caudate, lentiform nuclei & splenium of corpus callosum with corresponding FLAIR hyperintensity in dentate (black thick arrow). (b) DWI shows restricted diffusion in bilateral caudate, lentiform nuclei, splenium, dentate nuclei & subcortical white matter. (c) Complete resolution in follow-up MRI 4 weeks after stoppage of drug with complete clinical recovery.



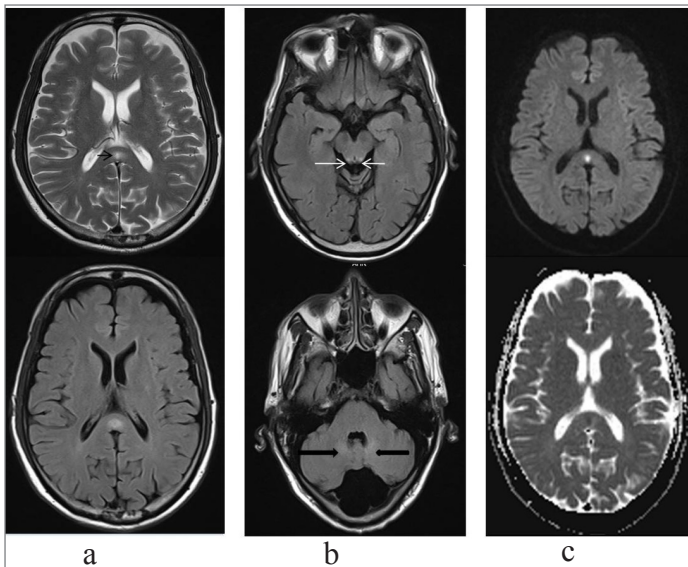
[Table/Fig-2]: A 50-year-old man had symptoms of sensori-motor neuropathy for past 8 months and altered sensorium for past 7 days. He had history of daily metronidazole intake for past 18 months & 1 week back, dose was increased to 2 gm/day. (a) T2W MRI shows splenium hyperintensity in axial (white thin arrow) and sagittal (black thin arrow) views. DWI and ADC maps show diffusion restriction & low ADC (black thick arrow), respectively, in the corresponding areas of corpus callosum. (b) Follow-up MRI 3 weeks after drug withdrawal shows complete resolution of lesions, and the patient also recovered of encephalopathy.



[Table/Fig-3]: A 40-year-old man had a sensori-motor neuropathy for last 8 years and recurrent episodes of slurring of speech and ataxia lasting for 10-12 hours for last 5 years. (a) T2W MRI sagittal view shows hyperintensities in genu and body of corpus callosum (white thin arrows) & axial view shows hyperintensities in genu (black thin arrows). (b) DWI and ADC maps show diffusion restriction and a high ADC respectively, in the corresponding areas of corpus callosum. Patient improved symptomatically 8 weeks after stoppage of metronidazole, however follow up imaging didn't show much change (only minimal resolution).

systemic lupus erythematosus, vitamin B12 deficiency, stroke, hypertensive encephalopathy, pre-eclampsia, hypoglycemia, hyponatraemia, renal failure, high altitudinal oedema and acute toxic encephalopathy (methotrexate and 5-fluorouracil) [38].

Diffusion restriction with low ADC has been noted in metabolic encephalopathies like Wernicke's encephalopathy [39] and maple



[Table/Fig-4]: A 69-year-old man, diagnosed as a case of amoebic liver abscess developed encephalopathy 7 days after initiation of treatment with metronidazole (2gm/day). (a) T2W MRI shows splenium hyperintensity (black thin arrow) which corresponds with the splenium hyperintensity on FLAIR sequence. (b) FLAIR images show faint dentate hyperintensities (black thick arrows) and inferior colliculi hyperintensities (white thin arrows). (c) DWI shows diffusion restriction in the splenium with low ADC value. Patient's symptoms resolved completely, one week after stoppage of metronidazole. (Follow up imaging not available)

syrup urine disease [37], and rarely in dysmyelinating disorders like Canavan disease [40].

Fortunately, clinical scenario, laboratory and other investigations can easily differentiate metronidazole toxicity from these disorders at majority of instances. In cases where doubt still remains, clinicians can withdraw metronidazole and observe the patients clinically and through serial imaging. In cases of metronidazole toxicity, clinical improvement and resolution of MRI changes is likely [41].

DIAGNOSIS

In view of lack of accurate diagnostic tool or criteria, diagnosis always depends upon high clinical suspicion, specific imaging abnormalities, ruling out other clinical and radiological differentials and significant improvement after prompt withdrawal of the offending agent.

FOLLOW-UP

Improvement in clinical symptoms after discontinuation of the drug is noticed in majority of cases [11]. However, reversibility is not a rule. Groothoff et al., and Hobbs et al., reported irreversible encephalopathy with metronidazole resulting into mortality [31,42]. In both the cases, patients remained on metronidazole therapy for some time (12 days and 14 days respectively) even after the appearance of initial neurological symptoms. Thus, rapid withdrawal should be a rule in cases where there is high index of suspicion. Mortality can occur even with low cumulative dose and peak concentration, so, other co-morbid factors may be contributory [42]. Impaired cognition in form of memory dysfunction and learning [43,44] and vegetative state [28] has also been reported as an outcome anecdotally. Time to improvement of symptoms varies from patient to patient and perhaps it depends upon multiple factors including severity of symptoms, duration of clinical features, underlying diseases, co-morbid factors and also imaging abnormalities. In majority of cases clinical and radiological improvement occurs after withdrawal of the drug and goes hand in hand. However, poor correlation between symptoms outcome and Magnetic Resonance Imaging (MRI) scans has also been noted [11].

The most remarkable feature of this disease is complete or near-complete resolution of the original lesions on follow-up MRIs [28]. Some researchers have postulated that initial lower values of ADC may predict poor outcome [45]. However, sometimes lesions persist despite an initial normal ADC value and hence it cannot be concluded with certainty that reversibility of the lesions depends on ADC values at presentation [43]. Researchers have noted that reduction of peaks of lactate after a follow-up time of 3 weeks can be used to differentiate it from a pure mitochondrial pathology [45]. It has also been hypothesized that there could be an anatomical basis of preference with respect to non resolution of lesions. Some areas like inferior olivary nuclei or splenium of corpus callosum have been reported earlier as sites of non resolution [28,29]. However, the persistence of inferior olivary hypertrophy as reported, may have resulted due to the interruption of the circuit of the Guillain- Mollaret triangle and not necessarily induced by metronidazole therapy [29]. So, it can be concluded from these findings that radiological non-resolution may be observed in cases where there is initial diffusion restriction with low ADC values and in lesions of corpus callosum specifically. Our experience regarding resolution has been mixed i.e. out of 3 patients who had lesions of corpus callosum, {2 in the splenium (one in isolation and other in conjugation with other areas) and one in the body and genu}, 2 resolved completely and in one case where there were lesions of genu and body, there was only partial resolution. ADC values were available only for 2 cases and were high in both of them including the case where genu and body was involved with partial improvement after drug withdrawal and also in the case where splenium was involved in isolation.

SPECIAL SITUATIONS

Evaluation of MIE becomes still more complicated in patients who have underlying liver dysfunction, especially in patients of hepatic encephalopathy or end-stage liver disease. Even in patients of liver abscess who are often treated with metronidazole, deterioration in sensorium sometimes may prompt the clinician to think in lines of hepatic encephalopathy, however, the actual culprit may be the drug itself.

Cheong et al., reported a MRI confirmed case of a 57-year-old gentleman who was earlier diagnosed as alcoholic cirrhosis with hepatic encephalopathy, was initiated with metronidazole 500mg three times daily for 25 days (cumulative 30 grams) and presented with ataxia, dysarthria, and confusion. He regained consciousness in 2 days and improved significantly on other parameters 2 weeks after withdrawal of metronidazole from the treatment chart [46].

Knorr et al., reported the case of progressively worsening dysarthria followed by aphasia, vomiting and a left-sided facial palsy in a 63-year-old male with End Stage Liver Disease (ESLD) secondary to hepatitis C. He presented after receiving 2-week course of metronidazole for recurrent *Clostridium difficile*-associated diarrhea. However after withdrawal of metronidazole, his symptoms improved and there was complete resolution of typical MRI changes which were observed earlier [7].

Another case of deteriorating encephalopathy in form of new-onset dysarthria, myoclonus, increase in gait ataxia and chorea after a few days of increase in metronidazole dose due to fear of worsening encephalopathy was reported in a 60-year-old male with chronic liver disease secondary to hepatitis C by Galvez et al., MRI lesions were classical in this case too, and resolved 1 week after discontinuation of metronidazole along with improvement of the clinical symptoms [14]. Similarly, researchers have also reported MIE in patients of liver abscess which may be a diagnostic dilemma until imaging drops some clue [30].

So, in patients who are provisionally diagnosed as MIE with existing liver dysfunction or hepatic encephalopathy, one should always rule out factors that precipitate or increase the severity

of encephalopathy such as constipation, bowel obstruction, ileus, dehydration, uraemia, gastrointestinal bleed, sepsis, non-adherence to lactulose or hepatocellular carcinoma [47]. Other drugs on the chart like CNS depressants should also be withdrawn in this scenario as impaired liver function could lead to accumulation of drugs which undergo hepatic clearance.

Another situation where MIE may be a difficult clinical diagnosis is in patients of brain abscess who are being treated with this drug. Bahn et al., reported a case of brain abscess who was started on intravenous metronidazole (2g daily) and ceftriaxone (daily dosage 8g) on empirical basis owing to negative growth on culture after stereotactic aspiration and developed new onset binocular horizontal diplopia due to bilateral 6th nerve palsy, tinnitus, dysphagia and left hemiparesis on 20th day of treatment. Abscess progression or its complications like infarct were suspected initially and a MRI brain was done which revealed high intensity signals in bilateral dentate nuclei of the cerebellum, medulla, pons, splenium of corpus callosum and right trigone of periventricular white matter with diffusion restriction and low ADC in these areas (except in dentate nuclei where there was no diffusion restriction), but MR angiography was normal. Metronidazole was withheld and symptoms gradually began to improve, with complete resolution of MRI lesions on follow up scan [33].

Yet more complicated situation of a diagnosed case of liver cirrhosis caused by chronic hepatitis B who had undergone two cycles of peg interferon α -2 β was reported by Jang et al., She developed headache 2 weeks following a dental treatment, for

which she was diagnosed as having cerebral abscess on brain MRI [48]. Pus was aspirated stereotactically and processed for microbial growth on culture, which revealed *Streptococcus sanguis*, *Peptostreptococcus*, and *Bacteroides* species. Hence, subsequent treatment with metronidazole was started. After an initial fall in neutrophil count metronidazole was withheld but was again re-administered later due to non response of the other antibiotic (1.5 g per day, total dosage, 156.5 g). After 11 weeks, the patient complained of depressed mood, nervousness, tingling sensation and weakness in the left extremities. Later, patient also developed ataxia and dysarthria. MRI revealed high-signal intensity in dorsal medulla, dentate nuclei, splenium and pons on T2-weighted image and fluid attenuated FLAIR imaging. Besides, there were asymmetric lesions in the midbrain, thalamus, putamen, and subcortical white matter on right side with diffusion restriction in the splenium, midbrain, and cerebral subcortical white matter (with low ADC at these sites). After discontinuation of metronidazole, the patient progressively recovered from the symptoms [48].

Nevertheless, neurosurgeons or physicians who treat brain abscess should be aware about this condition and special caution should be taken while selecting antibiotics for such patients. [Table/Fig-5] summarizes the different case studies of MIE worldwide.

MANAGEMENT

Withholding metronidazole as early as possible along with supportive therapy is the only proven measure. Furthermore, alternative

Country, Author, Year (in chronological order)	Age (Years) / Sex	Indication	Duration (days)	Cumulative Dose (grams)	Presentation	MRI Findings (T2 and FLAIR)	MRI Findings Diffusion restriction and ADC	Follow up MRI Findings (Weeks after)	Neurological Outcome
USA, Frytak et al., [2], 1978(3 cases)	77/F 75/F 52/F	Inoperable pancreatic carcinoma Hepatic and pulmonary metastasis of rectal carcinoma Sensitizer for metastatic carcinoma of the stomach	5 7 5	Not Mentioned 42 52	Seizures Seizures seizures	Not done	Not done	Not done	Resolution Resolution Resolution
USA, Kusumi et al., [1], 1980	45/F	<i>B. fragilis</i> anterior mediastinal abscess	28	84.0	Cerebellar dysfunction Alteration in mental status	Not done	Not done	Not done	Resolution
USA, Ahmed et al., [8], 1995	45/F	<i>Blastocystis hominis</i> diarrhea	30	35.0	Cerebellar dysfunction Alteration in mental status	Symmetric Hyperintensities in cerebellar nuclei, genu and splenium of the corpus callosum and within frontal and parietal subcortical white matter	Not mentioned	Complete and near complete normalization of lesions of corpus callosum and subcortical white matter respectively	Resolution
USA, Uhl et al., [49], 1996	65/F	Portosystemic encephalopathy	90	NS	Alteration in mental status	Not done	Not done	Not done	Resolution
USA, Horlen et al., [9], 2000	34/M	<i>B. fragilis</i> meningitis + Bacteremia	50	75.0	Cerebellar dysfunction Alteration in mental status	Hyperintensities in the inferior basal ganglia lateral to the hypothalamus and also below, behind, and lateral to the fourth ventricle	Not mentioned	Not done	Resolution
USA, Cecil et al., [21], 2002	17/M	Crohn disease	NS	NS	Cerebellar dysfunction	Symmetrical hyperintensities in the pars compacta of the substantia nigra, red nucleus, globus pallidus, putamen, caudate body, caudate heads and medial thalami. Faint contrast enhancement of the lesions in the red nucleus and cerebral peduncles. Proton MRS performed in the splenium and in the basal ganglia showed an elevated lactate resonance.	Not mentioned	Near-complete resolution of the previous abnormalities (after 13 weeks)	Resolution
USA, Woodruff et al., [50], 2002	74/M	Intra-abdominal abscesses	28	42.0	Cerebellar dysfunction	Hyperintensities in subcortical white matter and cerebellar dentate nuclei	Not mentioned	Complete normalization (after 5 weeks)	Resolution
Korea, Seok et al., [29], 2003	74/F	Rectovaginal fistula associated with Crohn disease	90	90.0	Cerebellar dysfunction	Hyperintensities in diffuse subcortical white matter, splenium, anterior commissure, basal ganglia, midbrain, cerebellar white matter and inferior olivary nuclei. (FLAIR)	Diffusion restriction in similar areas. ADC- Low	Complete normalization (after 17.5 weeks)	Near resolution

Country, Author, Year (in chronological order)	Age (Years) / Sex	Indication	Duration (days)	Cumulative Dose (grams)	Presentation	MRI Findings (T2 and FLAIR)	MRI Findings Diffusion restriction and ADC	Follow up MRI Findings (Weeks after)	Neurological Outcome
USA, Hearnay et al., [32], 2003	74/M	Abdominal purulent abscess	56	84.0	Cerebellar dysfunction	Hyperintensities in dentate nuclei, focal and confluent areas of nonenhancing signal intensity abnormality in the periventricular regions (believed to be related to chronic small vessel ischemic changes)	Diffusion restriction in dentate nuclei ADC-High	Complete normalization (after 8 weeks)	Resolution
Japan, Ito et al., [51], 2004	54/F	<i>H. pylori</i>	66	660.0	Cerebellar dysfunction	Hyperintensities in dentate nuclei	Not mentioned	Complete normalization (after 12 weeks)	Resolution
Korea, Kim et al., [43], 2004 (2 cases)	a. 31/M	a. Crohn disease.	a. 6 + chronic use	a. 3 times usual dose + chronic use	a. Alteration in mental status	Hyperintensities in subcortical white matter and cerebellar dentate nuclei	Diffusion Restriction only in the subcortical white matter ADC- Low	Complete normalization (after 8 weeks)	a. Impaired cognition
	b. 46/M	b. Acute Cholangitis	b. 6	b. Not Mentioned	b. Alteration in mental status	Hyperintensities in subcortical white matter and cerebellar dentate nuclei	Diffusion Restriction only in the subcortical white matter ADC- Low	Not mentioned	b. Vegetative state
Belgium, De Bleecker et al., [6], 2005	20/M	Ulcerative colitis	730	1110	Cerebellar dysfunction	Hyperintensities in splenium and less conspicuously in the truncus and genu of the corpus callosum	Not mentioned	Partial resolution of the previous abnormalities (after 8 months)	Impaired visual acuity
USA, Deenadayalu et al., [52], 2005	50/M	Peritonitis + hepatic Encephalopathy	5	7.5	Cerebellar dysfunction	Hyperintensities in cerebellar dentate nuclei	Not mentioned	Complete normalization (Time not mentioned)	Improvement
Korea, Kim et al., [28], 2007 (7 cases)	a. 54/M	a. Spontaneous bacterial Peritonitis	a. 15	a. 22.5	a. Cerebellar dysfunction Alteration in mental status	Hyperintensities in B/L dentate nuclei, dorsal medulla, vestibular nucleus, abducens nucleus, superior olivary nucleus, tegmentum of midbrain, red nucleus and corpus callosum	Diffusion restriction in peripheral part of dentate nuclei, central part of splenium, pons and midbrain ADC- low in splenium; rest areas- high.	Not available	a. Improvement
	b. 64/M	b. Intra-abdominal abscess	b. 17	b. 25.5	b. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, dorsal medulla, inferior olivary nucleus, vestibular nucleus, superior olivary nucleus, tectum and tegmentum of midbrain, corpus callosum and subcortical white matter	Not available	Complete normalization (After 2 weeks 3 days)	b. Improvement
	c. 55/M	c. Ischemic colitis	c. 11	c. 16.5	c. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, dorsal medulla, vestibular nucleus, abducens nucleus, superior olivary nucleus, tegmentum of midbrain, corpus callosum	Diffusion restriction in splenium and dentate nuclei ADC-Low in splenium and High in dentate	Complete resolution of the hyperintense lesions in the dentate and pons but residual hyperintensity in splenium (After 2 weeks)	c. Improvement
	d. 71/M	d. DM foot	d. 17	d. 25.5	d. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, dorsal medulla, vestibular nucleus, abducens nucleus, superior olivary nucleus and tectum	Diffusion restriction in dorsal medulla ADC-High	Complete normalization (After 5 weeks)	d. Improvement
	e. 61/F	e. Pseudomembranous colitis	e. 24	e. 36.0	e. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, tectum of midbrain	Diffusion restriction in tectum ADC- High	Not available	e. Improvement
	f. 49/M	f. Crohn disease	f. 52	f. 78.0	f. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, vestibular nucleus, abducens nucleus, superior olivary nucleus, tegmentum of midbrain and red nucleus	Diffusion restriction in tegmentum, red nucleus of midbrain and dorsal pons ADC- High	Complete normalization (After 2 weeks)	f. Improvement
	g. 70/M	g. Brain abscess	g. 22	g. 33.0	g. Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei, vestibular nucleus, superior olivary nucleus, tectum and tegmentum of midbrain, red nucleus and corpus callosum	Not available	Not available	g. Improvement
Tunisia, Hammami et al., [53], 2007	51/M	Anal fistula	21	31.5	Cerebellar dysfunction Alteration in mental status	Hyperintensities in B/L dentate nuclei, splenium, locus niger, periaqueductal region and bulbar region.	Diffusion restriction in dentate nuclei and splenium ADC- Low	Complete normalization (after 4 weeks)	Resolution
Canada, Sarna et al., [54], 2009 (2 cases)	a. 72/F	a. Intra-abdominal abscess	a. 25	a. 25.0	a. Cerebellar dysfunction	a. Hyperintensities in B/L dentate nuclei	Not mentioned	Complete normalization (after 4 weeks)	a. Resolution
	b. 54/M	b. Bronchiectasis	b. 60	b. 60.0	b. Cerebellar dysfunction, Seizure	b. Hyperintensities in B/L dentate nuclei	Not mentioned	Complete normalization (after 12 weeks)	b. Resolution

Country, Author, Year (in chronological order)	Age (Years) / Sex	Indication	Duration (days)	Cumulative Dose (grams)	Presentation	MRI Findings (T2 and FLAIR)	MRI Findings Diffusion restriction and ADC	Follow up MRI Findings {Weeks after}	Neurological Outcome
Korea, Lee et al., [30], 2009(9 cases)	a. 47/M	a. Decubitus ulcer	a. 50	a. 100	a. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus	Diffusion restriction was present in similar areas in 4 patients, in other 2 patients the sites of diffusion restriction and sites of T2/FLAIR hyperintensity did not match.	a. Not available	a. Improvement
	b. 61/M	b. Liver abscess	b. 60	b. 120	b. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, Corpus Callosum	ADC- obtained in 4 patients; In 3 patients low values were obtained in dentate, splenium and inferior colliculus and in 1 patient high value was noted in dentate nucleus	b. Complete normalization except for lesion of corpus callosum {After 3 days}	b. Improvement
	c. 76/F	c. Liver abscess	c. 50	c. 100	c. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus,		c. Complete normalization {After 8 days}	c. Improvement
	d. 78/F	d. Lung abscess	d. 40	d. 80	d. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus, corpus callosum, cerebral white matter		d. Not available	d. Improvement
	e. 64/F	e. Peritoneal abscess	e. 50	e. 100	e. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus, Pons		e. Complete normalization {After 15 days}	e. Improvement
	f. 68/M	f. Lung abscess	f. 44	f. 88	f. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus		f. Complete normalization {After 4 days}	f. Improvement
	g. 60/M	g. Brain abscess	g. 60	g. 120.0	g. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus, medulla		g. Complete normalization {After 15 days}	g. Improvement
	h. 43/M	h. Peritoneal abscess	h. 30	h. 45	h. Cerebellar dysfunction	Hyperintensities in b/l dentate nucleus, inferior colliculus, pons		h. Not available	h. Improvement
UK, Graves et al., [55], 2009	61/M	<i>Klebsiella</i> wound infection	77	92.4	Cerebellar dysfunction	Hyperintensities in cerebellar dentate nuclei	Not mentioned	Not done	Resolution
Chile, Galvez et al., [14], 2009	60/M	Hepatic encephalopathy (Known case of Hepatitis C)	Not Mentioned	Not Mentioned	Cerebellar dysfunction, increase in gait ataxia, chorea of the face and limb and myoclonus	FLAIR image- Hyperintense lesions on cerebellum dentate nuclei. T2-weighted images - hyperintense lesions involving the bilateral cerebellum dentate nuclei, inferior colliculus, and corpus callosum	Diffusion-restriction in cerebellar dentate nuclei and inferior colliculus	Complete resolution of the hyperintense lesions in the cerebellum and brainstem (after 4 weeks)	Improvement
Korea, Bahn et al., [33], 2010	52/M	Brain Abscess	20	40	Cerebellar dysfunction	Hyperintensities in B/L dentate nuclei of cerebellum and splenium	Diffusion-restriction in pons, splenium, and the right trigone periventricular white matter ADC- low in the splenium and right trigone periventricular white matter	Complete normalization	Resolution
Netherlands, Groothoff et al., [31], 2010	38/F	<i>B. fragilis</i> wound of Osteomyelitis	70	132.0	Cerebellar dysfunction alteration in mental status, seizures	FLAIR Hyperintensities in bilateral centrum semiovale and cerebellar peduncles.	Not mentioned.	No improvement (CT scan at 7 week)	Died
India, Kalia et al., [56], 2010	43/M	Amoebic liver abscess	60	72.0	Cerebellar dysfunction	Symmetrical hyperintensities of dentate nuclei, dorsal pons, and splenium	Diffusion restriction in similar areas. ADC- Low	Not available	Resolution
Korea, Cheong et al., [46], 2011	57/M	Alcoholic cirrhosis, hepatic encephalopathy	26	30	Cerebellar dysfunction, alteration in mental status	Hyperintensity in B/L dentate nuclei, splenium	Diffusion restriction in corpus callosum ADC: Not Mentioned	Complete normalization {after 5 weeks}	Resolution
Sweden, Khodakaram et al [57], 2011	50/M	Abscess of appendix	7	8	Cerebellar dysfunction, loss of hearing and vertigo	Hyperintensity in B/L dentate	Not Mentioned	Complete normalization {after 8 weeks}	Resolution
Korea, Park et al., [58], 2011	67/M	Liver abscess	83	127.5	Cerebellar dysfunction	Hyperintensity in B/L dentate nuclei, splenium (FLAIR)	Diffusion restriction in Splenium; ADC: low	Near normalization of dentate, but residual hyperintensity of splenium (FLAIR and DWI); Normalization of ADC {after 1 week}	Improvement
Japan, Yamamoto et al., [59], 2012	68/M	Liver Abscess	19	28.5	Cerebellar dysfunction, alteration in mental status	Hyperintensity in B/L dentate nuclei, (and hyperintensity of basal ganglia on T1)	Not Mentioned	Complete normalization of dentate lesions, basal ganglia lesions: Not Mentioned {after 4 weeks}	Resolution
Korea, Jang et al., [48], 2012	60/F	Anaerobic Brain Abscess (known case of Chronic hepatitis B, Liver cirrhosis)	77	171.5	Cerebellar dysfunction, hemiparesis	Hyperintensity in B/L dentate nuclei, dorsal medulla, pons, splenium, asymmetric lesions in midbrain, thalamus, putamen, subcortical white matter	Diffusion restriction in splenium, midbrain, thalamus, subcortical white matter. ADC low in subcortical white matter	Complete normalization except for lesion of splenium {after 4 weeks}	Resolution
USA, Knorr et al., [7], 2012	63/M	Clostridium difficile associated diarrhea (Known patient of ESLD with Hepatitis C)	14	7.5	Cerebellar dysfunction, diplopia, facial palsy	Hyperintensity in B/L dentate nuclei, inferior colliculi and splenium	Diffusion restriction in the splenium	Complete normalization {after 6 weeks}	Resolution
Turkey, Erdener et al., [41], 2013	64/F	Ulcerative colitis	315	450	Intermittent ataxia and dysarthria	Hyperintensity of corpus Callosum, dentate nuclei	Diffusion restriction of corpus Callosum, ADC- low	Complete normalization of lesions of Dentate nuclei, Less prominent hyperintensity of corpus callosum, cystic degeneration in the genu of the corpus callosum. {13 weeks later}	Not Mentioned

Country, Author, Year (in chronological order)	Age (Years) / Sex	Indication	Duration (days)	Cumulative Dose (grams)	Presentation	MRI Findings (T2 and FLAIR)	MRI Findings Diffusion restriction and ADC	Follow up MRI Findings (Weeks after)	Neurological Outcome
India, Iqbal et al., [60], 2013	78/M	Amoebic liver abscess	35	84	Cerebellar dysfunction, headache and Seizures	Hyperintensity in B/L dentate nuclei, dorsal midbrain and pons	Diffusion restriction in B/L dentate nuclei, dorsal midbrain and pons, ADC-Normal	Complete normalization {12 days later}	Improvement
USA, Godfrey et al., [61], 2015	65/F	<i>Clostridium difficile</i> colitis	42	63	Alteration in mental status	Hyperintensity in B/L dentate nuclei, superior cerebellar peduncle, splenium and parietal subcortical white matter	Diffusion restriction in superior cerebellar peduncle, splenium and parietal subcortical white matter	Resolution of signal intensity of cerebellar peduncles and dentate nuclei {17.5 weeks later}	Resolution
India, Haridas et al., [62], 2015	51/F	Irritable bowel syndrome	5	7.5	Alteration in mental status	Hyperintensity in B/L dentate nuclei	Not Mentioned	Not done	Resolution
Japan, Yagi et al., [15], 2015	36/M	Intractable pulmonary empyema (Known case of Alcoholic liver cirrhosis)	21	42	Cerebellar dysfunction, Alteration in mental status, Myoclonus	Hyperintensities of Dentate nucleus, superior cerebellar peduncles, dorsal pons, periaqueductal area, splenium of the corpus callosum (FLAIR)	Diffusion restriction in similar areas hyperintense in FLAIR	Reduction in hyperintensities {at 9 weeks}	Myoclonus disappeared 3 days after the discontinuation of Metronidazole. There was slight neurological improvement, but deteriorated due to liver failure and died about 2 months later
India, Senthilkumaran et al., [63], 2015	39/M	Amoebic liver abscess	28	67.2	Cerebellar dysfunction, alteration in mental status	Hyperintensity in B/L dentate nuclei, splenium	Diffusion restriction in B/L dentate nuclei, splenium	Complete normalization {17.5 weeks later}	Resolution
USA, Hobbs et al., [42], 2015	69/F	Spontaneous bacterial peritonitis, gangrenous cholangitis (known case of Chronic hepatitis B, Liver cirrhosis)	22	33	Alteration in mental status	B/L symmetrical hyperintensities of subcortical white matter, corpus callosum, internal capsule, midbrain, superior cerebellar peduncles and bilateral dentate nuclei	Perfusion arterial spin labeling revealed hyperintensity in bilateral dentate nuclei.	Relative improvement of Diffusion restriction in the dentate nuclei but persistent T2 hyperintensity in this area. New restricted diffusion in the cortex in a middle cerebral artery-posterior cerebral artery border zone pattern bilaterally, right worse than left. Perfusion arterial spin labeling imaging demonstrated hyperperfusion of uncertain significance in these regions. { 1 week later}	Died on hospital day 31 (24 days from metronidazole discontinuation).
Japan, Furukawa et al., [34], 2015	52/M	Retroperitoneal abscess	120	250	Cerebellar dysfunction, cognitive impairment	Hyperintense lesions in the bilateral cerebellar dentate nucleus, corpus callosum, and subcortical white matter . Multiple contrast-enhanced T1-weighted lesions observed in the corpus callosum.	Diffusion- Not mentioned. ADC-low in corpus callosum and white matter	Near normalization of lesions in the bilateral dentate nucleus, and decrease in size of lesions in corpus callosum and white matter , Multiple cystic lesions in the corpus callosum and bilateral white matter	Improvement
India, Roy et al., 2015(<i>this study-4 cases</i>)	43/M	Recurrent Amoebic dysentery(1 st episode resolved after 7 days of therapy but recurred after a gap of 1 week)	6	15.6	Cerebellar dysfunction, alteration in mental status	Hyperintense lesions in the bilateral cerebellar dentate nucleus, splenium of corpus callosum, bilateral caudate head and body, lentiform nuclei and inferior olive, and subcortical white matter .	Diffusion restriction in bilateral cerebellar dentate nucleus, splenium of corpus callosum, bilateral caudate head and body, lentiform nuclei and subcortical white matter. ADC-Not available	Complete normalization {4 weeks later}	Resolution
	50/M	Irritable bowel syndrome(chronic intermittent intake(~400 mg/day)-self medication for 18 months), recent increase in dose(2g/day)	~554	244	Alteration in mental status, peripheral neuropathy	Hyperintense lesions in the splenium of corpus callosum	Diffusion restriction in splenium of corpus Callosum ADC-Black	Complete normalization {3 weeks later}	Resolution of alteration in sensorium and improvement in symptoms of neuropathy
	40/M	Irritable bowel syndrome(chronic intermittent intake(~400 mg/day)-self medication for 8 years)	~2848	1139.2	Episodic dysarthria and ataxia, peripheral neuropathy	Hyperintense lesions in the genu and body of corpus callosum	Diffusion restriction in the genu and body of corpus callosum ADC-White	Minimal Resolution {8 weeks later}	No further episodic ataxia and improvement in symptoms of neuropathy
	69/M	Amoebic liver abscess	7	14	Cerebellar dysfunction, alteration in mental status	Hyperintense lesions in the bilateral cerebellar dentate nucleus (faint), splenium of corpus callosum, and inferior colliculus.	Diffusion restriction in splenium of corpus callosum ADC-Black	Not available	Resolution

[Table/Fig-5]: Case studies of Metronidazole induced encephalopathy

M- male, F-female, Cerebellar dysfunction- Dysarthria, ataxia, ESLD-End Stage Liver Disease, B/L- Bilateral, ADC- Apparent diffusion coefficient, FLAIR- Fluid-attenuated inversion recovery

therapy may be started for the initial infection depending upon the culture and antibiotic sensitivity report from the respective specimen. For example, in cases of *clostridium difficile* associated diarrhea oral vancomycin may be started. Similarly in cases of hepatic encephalopathy metronidazole should be replaced with oral vancomycin, paromomycin, oral quinolones, or rifaximin and patients with *H. pylori* infection may be put on antibiotic regimens containing lansoprazole, amoxicillin, and clarithromycin. Nevertheless, where a 5-nitroimidazole is indispensable, replacement with other 5-nitroimidazole like tinidazole or ornidazole may be tried, however, similar side effects have been observed with these drugs too [27]. Though there has been a positive report of diazepam as a measure to shorten time of recovery in dogs, no such reports are published in case of human beings [18].

OUR EXPERIENCE

We recently encountered 4 cases of MIE in outpatient and emergency departments [Table/Fig-1-5]. We observed some distinct features of this entity which need to be highlighted. Two out of 4 patients we encountered were on long-term metronidazole therapy by self medicating themselves with over the counter medications for presumed irritable bowel syndrome. Similar history of over-the-counter self-medication was reported by Haridas et al., [62]. Nevertheless, self-medication and chronic intake seems to be a common entity, at least in this part of the globe. It is worth to emphasize here that one patient initially denied any history of previous drug intake, it was only after looking at the MRI brain and ruling out other differentials that we suspected metronidazole intoxication. Further, on specific questioning he revealed that he had been taking this drug quite for a long time and thought this drug as a 'self remedy' for 'abdominal problems' which was later diagnosed as irritable bowel syndrome. Another striking feature we noted was that in all the 4 cases, corpus callosum was involved. Interestingly, one case had isolated involvement of genu and body which has not been reported in literature previously. We also noticed in the same patient that despite high ADC values patient's lesion did not resolve up to much extent which may be due to necrotic degeneration as a result of chronic insult and subsequent gliosis. Hence, perhaps the duration of the drug intake also determines reversibility of lesion on MRI.

CONCLUSION

Apart from peripheral neuropathy metronidazole can also cause symptoms of central nervous system dysfunction like ataxic gait, dysarthria, seizures, and encephalopathy. Due to its wide availability and frequent use, metronidazole is one of the commonly used over the counter medications, hence, in cases where clinical suspicion is high, drug history should be sought properly. Clinicians should order an MRI scan of brain whenever indicated and be aware of typical and atypical sites of involvement. All the typical sites may not be involved on MR imaging in every case, so clinical correlation and other relevant investigations should be combined for a rational approach. Reversibility of lesions after discontinuation of the offending agent may be helpful for clinching the diagnosis in clinically suspected or doubtful cases. Special precaution should be taken while starting metronidazole therapy in patients with underlying liver dysfunction, hepatic encephalopathy and patients with brain abscess. Clinicians should closely monitor physical signs in these cases and order an imaging wherever there is high index of suspicion of intoxication. Wherever in doubt, a trial of withdrawal is a rational approach, unless there is dire indication, as early stoppage of this drug may lead to complete recovery as opposed to patients in whom there is substantial delay in withholding therapy with metronidazole.

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