REVIEW ARTICLE

Neurologic Complications of Metronidazole

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ABSTRACT: Metronidazole (Flagyl®) is an antimicrobial agent commonly used in clinical practice. Although it is generally well tolerated with minimal side effects, there are a host of still under-recognized neurologic complications of metronidazole treatment. The following review is aimed at summarizing current literature pertaining to metronidazole-induced neurotoxicity including clinical syndromes, neuroradiological findings, prognosis and proposed pathophysiology. Recognition of the neurotoxic effects of metronidazole is critical as prompt discontinuation is generally associated with full clinical recovery and radiological resolution.

RÉSUMÉ: Complications neurologiques du métronidazole. Le métronidazole (Flagyl®) est un agent antimicrobien utilisé couramment en pratique clinique. Bien qu'il soit généralement bien toléré et que ses effets secondaires soient minimes, il existe une myriade de complications neurologiques du traitement par le métronidazole qui ne sont pas toujours reconnues. Le but de cette revue constitue un sommaire de la littérature actuelle concernant la neurotoxicité induite par le métronidazole dont les syndromes cliniques, les constatations neuroradiologiques, le pronostic et l'hypothèse physiopathologique expliquant cette neurotoxicité. Il est important d'identifier ces effets neurotoxiques du métronidazole étant donné que l'arrêt immédiat du traitement est généralement associé à une guérison clinique complète et à la disparition des signes radiologiques.

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Metronidazole (Flagyl®; 1-(β-hydroxy-ethyl)-2-methyl-5-nitroimidazole) is an antiprotozoal and antimicrobial agent commonly used in clinical practice. It was first introduced in 1959 for the treatment of *Trichomonas vaginalis*[1]. Although metronidazole is usually well tolerated, common side effects include metallic taste, nausea, vomiting, diarrhea, abdominal cramps, dark urine, headache, dizziness and disulfram-like reaction with exposure to alcohol[1].

Metronidazole is primarily metabolized by the liver with peak serum levels of the drug (between 20 to 80 μg/mL) achieved within one hour of oral administration of recommended doses of 1 to 2 g/day[2,3]. It is a lipophilic compound that readily crosses the blood-brain barrier[4], is renally excreted, and has a half life of approximately eight hours[1].

Chronic metronidazole administration is not limited to the treatment of refractory infections – its use has become widespread in the context of a variety of clinical scenarios. The first is in the management of hepatic encephalopathy when treatment with lactulose alone is insufficient[5]. Second, metronidazole is used in the treatment of inflammatory bowel disease (IBD) as enteric flora are thought to contribute to its pathogenesis (e.g.,[6]). Finally, and purely from a historical perspective, high doses of metronidazole were evaluated as a potentiating agent in radiotherapy but it was subsequently found to be ineffective[7,8].

Metronidazole can be neurotoxic and produce a variety of neurologic syndromes including a cerebellar syndrome, encephalopathy, seizures, and optic, autonomic and peripheral neuropathies (Table 1). As many of the neurologic syndromes are fully reversible upon discontinuation of the drug, it is likely that metronidazole's neurotoxicity may not be recognized or reported. We previously described two cases with a cerebellar syndrome following prolonged exposure to metronidazole[9]. This

Table 1: Known neurological side effects of metronidazole (Adapted from[9]).

Neurological side effects of metronidazole
Cerebellar syndrome
Encephalopathy
Seizures
Optic neuropathy
Autonomic neuropathy
Peripheral neuropathy

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Table 2: Summary of case reports of metronidazole-induced cerebellar syndrome.

Reference	n	Age, Sex	Cumulative Dose (g)	Duration (d)	Resolution	Imaging
Ahmed et al., 1995 (11)	1	45, F	31.5g	30d	Resolution of symptoms within 1 week (symptoms: confusion, ataxia, sensory changes, vertigo, tinnitus, hearing loss)	CT: normal T2 signal: DCN and supratentorial WM including CC. (imaging almost normalized within 6 weeks)
Alvarez et al., 1983 (12)	1	20, F	25.5g	18d	Symptoms resolved	n/a
Bonkowsky et al., 2007 (13)	1	27, M	n/a	14d	Resolution of symptoms within 3 weeks (symptoms: confusion, ataxia)	DCN, dorsal pons and medulla; resolution in 6 wks (no enhancement) 6 wk f/u MRI: resolution
Chatzkel and Vossough, 2010 (14)	1	15, F	n/a	7d	n/a (clinical resolution not discussed)	T2/FLAIR hyperintensities within dentate nuclei f/u MRI: complete resolution
De Bleecker et al., 2005 (15)	1	20, M	1095g	2yrs	(symptoms: sensory x 1 yr; ataxia x 2 mo; visual loss x 2 wks) marked improvement in vision and ataxia in 2 wks; sensory symptoms resolved w/t 3 months	MRI: T2/FLAIR signal hyperintensities within the splenium of the corpus callosum
Deenadayalu et al., 2005 (16)	1	50, M	7.5g	5d	Cerebellar syndrome only 5 days of tx Pt had hepatic encephalopathy Clinical improvement 2 wks post d/c	CT: normal MRI: symmetrical hyperintensities within the dentate nuclei. f/u MRI: complete resolution
Galvez et al., 2009 (17)	1	60, M	n/a	n/a	Chronic liver disease (Hepatitis C) Ataxia, myoclonus and worsening encephalopathy within days of increased dose of metronidazole Clinical improvement within 1 week	MRI: symmetrical T2 hyperintensities within the dentate nuclei, corpous callosum, inferior colliculi, caudal medulla f/u MRI: complete resolution
Graves et al., 2009 (18)	1	61, M	92.4g	77d	Multiple transplant patient Toxic metronidazole level Complete clinical resolution 8 wks later	CT: normal MRI: symmetrical T2/FLAIR hyperintensities
Gupta, 2003 (19)	1	50, M	200g	84d	Cerebellar syndrome and severe peripheral neuropathy Clinical improvement and resolution in cerebellar syndrome but not neuropathy	CT: hypodense areas in the cerebellum
Heaney et al., 2003 (20)	1	74, M	75g	56d	Cerebellar syndrome and peripheral neuropathy (lower extremities only)	CT: no acute changes (old lacunes) MRI: T2/FLAIR hyperintensities w/t dentate nuclei; minimal T1 hypointensity; no gad enhancement; T2 shine-through on ADC. F/U MRI at 8 wks: complete resolution of signal changes
Horlen et al., 2000 (21)	1	35, M	60g	55d	Pt with liver cirrhosis; developed cerebellar syndrome and peripheral neuropathy on metronidazole treatment Toxic metronidazole level Resolution not reported	MRI: signal changes within the dentate
Ito et al., 2004 (22)	1	54, F	66g		Cerebellar syndrome Resolution of symptoms within one week	MRI: T2/FLAIR hyperintensities within the dentate MRI at 8 days: marked improvement MRI at 3 months: complete resolution
Kalia et al., 2010 (23)	1	43, M	72g	60d	Cerebellar syndrome	MRI: T2/FLAIR hyperintensities within the dentate, dorsal pons and splenium of the corpus callosum; restricted diffusion on DWI
Kusumi et al., 1980 (10)	1	45, F	84g	28d	Encephalopathy, cerebellar syndrome and painful peripheral neuropathy Encephalopathy and cerebellar findings resolved w/t 6 days F/U at 7 months: resolution of neuropathy	CT: normal
Lawford and Sorrell, 1994 (24)	1	30, M	21g	14d	Cerebellar syndrome 1 day after d/c metronidazole. Resolution 1 month later Another episode months later after only 2 days of metronidazole – vertigo, unilateral deafness and ataxia	CT: normal
Moosa and Perkins, 2010 (25)	1	52, M	37.5g	35d	Cerebellar syndrome Complete resolution within 2 weeks of d/c metronidazole	MRI: T2/FLAIR hyperintensities (and mild T1 hypointensities) within the dentate nuclei, inferior olivary nuclei, central tegmental tracts, dorsal medullar and pons. No restricted diffusion or enhancement.
Patel et al., 2008 (26)	1	63, M	84g	42d	Cerebellar syndrome and ?mild peripheral neuropathy	MRI: T2/FLAIR hyperintensities withint he dentate f/u MRI at
Sarna et al., 2009 (9)	2	54, M	60g	60d	Cerebellar syndrome, seizures and peripheral neuropathy. Complete resolution at 3 month follow-up	MRI: T2/FLAIR hyperintensities within the dentate nuclei
		72, F	25g	21d	Cerebellar syndrome Resolution w/t weeks	MRI: T2/FLAIR hyperintensities within dentate nuclei. Resolution at follow-up MRI
Takase et al., 2005 (27)	1	69, M	75g	50d	Cerebellar syndrome **(unilateral)** and peripheral neuropathy Complete resolution at 1 month	MRI: T2/FLAIR hyperintensities within the dentate nuclei; **more marked in left hemisphere** SPECT: reduced perfusion in **left hemisphere** f/u MRI at 1 month: resolution
Toumi et al., 2008 (28)	1	27, M	60g	n/a	Cerebellar syndrome and peripheral neuropathy	MRI: T2/FLAIR hyperintensities within dentate nuclei Resolution at follow-up MRI
Woodruff et al., 2002 (29)	2	62, M	60g	30d	Cerebellar syndrome Complete resolution at 5 week follow-up	MRI: T2/FLAIR hyperintensities within dentate nuclei Resolution at follow-up MRI
		74, M	42g	28d	Cerebellar syndrome Improvement in 2 weeks	MRI: T2/FLAIR hyperintensities within dentate nuclei. Resolution at follow-up MRI

review is aimed at summarizing current literature pertaining to neurologic toxicity produced by this widely used antibiotic, including clinical syndromes, neuroradiological findings, prognosis and proposed pathophysiology. Case reports of metronidazole toxicity were identified through a PubMed search.

Clinical Syndromes: 1. Cerebellar Syndrome

The cerebellar syndrome induced by metronidazole was first described by Kusumi et al more than 30 years ago[10]. Their patient was a 45-year-old female who received a cumulative dose of 84g of metronidazole over 28 days for the treatment of

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an anterior mediastinal abscess. She developed a global cerebellar syndrome as well as a painful peripheral neuropathy. Although the cerebellar syndrome resolved six days post discontinuation of antibiotic treatment, neuropathic symptoms persisted for four months[10].

Since the initial description, there have been many similar case reports (summarized in Table 2;[9-29]). The cerebellar syndrome typically consists of dysarthria, gait and appendicular ataxia, nystagmus and saccadic pursuit. The ataxia is typically symmetrical save one case report[27] which described a patient with more severe involvement on one side correlating with greater T2 hyperintensity within the dentate nucleus and lower blood perfusion ipsilaterally in the cerebellum . The cumulative dose in these various case reports ranges widely from 7.5 g[16] to 1095g[15] suggesting individual patient vulnerability. Duration of treatment resulting in the cerebellar syndrome generally consists of at least one to two months (e.g.,[9,11,20,23]) although the syndrome can result from a shorter course of treatment[16]. No obvious risk factors have been identified other than pre-existing hepatic encephalopathy with end-stage liver cirrhosis[16]. Systemic clearance of metronidazole was shown to be reduced in patients with hepatic dysfunction[30] and Horlen et al[21] also implicated this as a contributing cause in their description of a cerebellar syndrome in a patient with liver cirrhosis.

With metronidazole discontinuation, recovery is gradual and fully reversible within days (e.g.,[10]) to weeks (e.g.,[13,18,27]) .

Computed tomogram (CT) head in patients with this cerebellar syndrome is typically normal except for one case report describing cerebellar hypodensities[19]. Typical magnetic resonance (MR) changes in this same group of patients show characteristic bilateral symmetric T2/FLAIR hyperintensities within the dentate nuclei with no mass effect or enhancement (e.g.,[9]). These radiological features resolve with drug discontinuation and parallel clinical recovery.

Approximately one third of the described patients with a metronidazole-induced cerebellar syndrome also present with concurrent peripheral neuropathy (e.g.,[19-21]) and, occasionally, with encephalopathy (e.g.,[10]). Therefore, metronidazole-induced neurotoxicity likely represents a spectrum of neurological involvement rather than distinct clinical syndromes.

Clinical Syndromes: 2. Encephalopathy

Metronidazole-induced encephalopathy can range from confusion (e.g.,[31]) to decreased level of consciousness and even coma (e.g.,[32,33]). (Some reports in the literature, however, use the term encephalopathy to describe any central nervous system toxicity induced by metronidazole even when there are no specific changes in mental status. For consistency, cases labeled as 'encephalopathy' in the literature were included in this group even if by clinical description they appear to have an isolated cerebellar syndrome). Correspondingly, patients with metronidazole-induced encephalopathy appear to have more widespread involvement of the brain on MR imaging, in comparison to the aforementioned cerebellar syndrome. Thus, in addition to symmetrical signal abnormalities within the dentate nuclei, patients with metronidazole-induced encephalopathy can show T2 weighted changes in the subcortical white matter, basal ganglia, corpus callosum (splenium portion in particular) and brainstem[31,34,35]. Generally, clinical and radiological features of encephalopathy are fully reversible upon discontinuation of metronidazole within days (see Table 3;[31-45]).

However, three patients presented with severe encephalopathy and did not recover[32,33]. One of these patients had atypical features on the MRI that included signal changes within the centrum semiovale and middle cerebellar peduncles[32] and presented to medical care after two weeks of ongoing symptoms including dysarthria, somnolence and eventually coma. She had received off-label dosing of intravenous metronidazole as an outpatient (1.5g IV once daily) and presumably high peak serum doses may have contributed to the severity of her presentation and poor prognosis. Another two patients described by Kim et al[33] included a patient that remained in a persistent vegetative state at six months despite only receiving a six-day course of metronidazole and another patient who improved clinically but did not fully recover even at a ten month follow-up. The daily and/or cumulative dose of metronidazole is not known for these cases.

Individual variability of patients to both cumulative dose and duration of treatment is also evident in this subgroup of patients (see Table 3). Although most descriptions of metronidazole-induced encephalopathy include prolonged (two to six months) exposure of 1.5 to 2 g daily, some patients develop symptoms in less than one week (e.g.,[33,36,43]). As with the cerebellar syndrome, the reason for this variability is uncertain.

Clinical Syndromes: 3. Seizures

Metronidazole may produce a variety of seizure semiology including (summarized in Table 4;[45-50]) myoclonus evolving into generalized seizures[46], generalized tonic clonic seizures[47,50] and seizures associated with obtundation and encephalopathy[45,48].

The electroencephalography (EEG) in this group of patients is typically normal (e.g.,[47]) or may reveal an encephalopathic picture with diffuse slowing but no focal abnormalities (e.g.,[45,46]). Cumulative doses of metronidazole ranged from 20.7g[48] to 165g[50] on relatively short course of the antimicrobial. Wienbren et al[45] describe a patient with seizures starting five days after metronidazole was discontinued and persisting in the first 24 hours despite a phenytoin load.

Some of the reported cases used high daily doses of metronidazole (up to 10.4 g daily) when it was still being utilized as a radiation sensitizer[47]. Therefore, high peak doses of metronidazole may potentially decrease seizure threshold. However, metronidazole levels within the cerebrospinal fluid do not directly correlate with likelihood of seizures[47]. As most of the studies reporting metronidazole-induced seizures are older, there is a lack of radiological correlation in this subgroup of patients other than a normal CT head in some of the cases[45,47].

In patients with metronidazole induced seizures, there may be overlap with other metronidazole-induced clinical syndromes as was the case in our patient[9] with concurrent cerebellar syndrome, worsening peripheral neuropathy and seizures who showed characteristic isolated dentate nuclei hyperintensities on MRI. Importantly, there are no reported cases of ongoing seizures after metronidazole discontinuation.

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Table 3: Summary of case reports of metronidazole-induced encephalopathy. Cases described in the literature as cerebellar syndrome but labeled as encephalopathy are indicted by asterisks (*)

Reference	n	Age, Sex	Cumulative Dose (g)	Duration (d)	Resolution	Imaging
Arik et al., 2001 (36)	1	58, F	n/a	2d	Prompt resolution of symptoms	CT: normal. MRI: atrophy and ischemic changes
Bottenberg et al., 2011 (34) *	1	55, M	~1095g	~2yrs	Cerebellar syndrome and peripheral neuropathy Complete resolution at 5 days post d/c of metronidazole	CT: normal. MRI: signal changes within the dentate, dorsal pons, inferior olivary nuclei and splenium of the corpus callosum. f/u MRI at 20 days: complete resolution of signal changes
Cazals et al., 2010 (37)	1	51, M	96g	64d	Resolution of symptoms 1 week after d/c of metronidazole	MRI: T2 hyperintensities involving dentate nuclei, superior and inferior cerebellar peduncles, central tegmental tract and inferior olives. f/u MRI at 5 weeks: complete resolution of signal changes
Cheong et al., 2011 (31)	1	57, M	30g	~36d	Confusion and cerebellar syndrome Encephalopathy resolved within 2 days of d/c of metronidazole	CT: increased density within the corpus callosum MRI: T2/FLAIR within the dentate nuclei and splenium of the corpus callosum; DWI – vasogenic edema within corpus callosum. f/u MRI at 5 weeks: complete resolution
Desai et al., 2011 (38)	1	74, M	n/a	~180d	Encephalopathy, cerebellar syndrome and large fiber peripheral neuropathy Resolution of symptoms at 6 weeks except for residual parasthesiae	MRI: restricted diffusion within the splenium of the corpus callosum with subtle prolongation of T2 f/u MRI at 5 months: resolution of restricted diffusion with residual prolongation of T2
Groothoff et al., 2010 (32)	1	38, F	132.5g	73d	Encephalopathy/decreased LOC, seizures. No clinical improvement at 8 weeks – withdrawal of care	CT: widened ventricles MRI: signal changes within centrum semiovale and cerebellar peduncles
Kim et al., 2004 (33)	2	31, M	n/a	?7d	Encephalopathy – drowsiness, inability to follow commands Marked improvement but not full resolution following d/c of metronidazole at 10 month follow-up	CT: normal. MRI: T2/FLAIR hyperintensities in dentate nuclei and subcortical white matter; restricted diffusion on DWI/ADC. f/u MRI at 2 months: resolution of dentate nuclei and restricted diffusion but residual hyperintensities within the subcortical white matter
		46, M	n/a	6d	Comatose Remained in persistent vegetative state at six month follow-up	MRI: T2/FLAIR hyperintensities within subcortical white matter and dentate nuclei; restricted diffusion within the subcortical white matter
Kim et al., 2007 (40)*	7	49, M	135g	90d onset at 52d	Cerebellar syndrome and ?peripheral neuropathy Clinical improvement at 10 days	MRI: T2/FLAIR hyperintensities within the dentate, pons (vestibular, abducens, superior olivary nucleus) and midbrain (tegmentum, red nucleus)
		70, M	57g	38d onset at 22d	Cerebellar syndrome and ?peripheral neuropathy Clinical improvement at 7 days	MRI: T2/FLAIR hyperintensities within the dentate, pons (vestibular and superior olivary nuclei), midbrain (tectum, tegmentum, red nucleus) and corpus callosum
		64, M	37.5g	25d onset at 17d	Cerebellar syndrome and ?optic neuropathy Clinical improvement at 7 days	MRI: T2/FLAIR hyperintensities within the dentate, medulla (dorsal, inferior olivary nucleus), pons (vestibular and inferior olivary nucleus), midbrain (tectum and tegmentum), corpus callosum and subcortical white matter f/u MRI at 17 days: complete resolution
		54, M	49.5	33d onset at 15d	Encephalopathy – confusion, dysarthria Clinical improvement at 5 days	MRI: T2/FLAIR hyperintensities within the dentate, medulla (dorsal), pons (vestibular, abducens, inferior olivary nuclei), midbrain (tegmentum and red nucleus) and corpus callosum
		71, M	66g	44d onset at 37d	Cerebellar syndrome Clinical improvement at 4 days	MRI: T2/FLAIR hyperintensities within the dentate, medulla (dorsal), pons (vestibular, abducens, inferior olivary nuclei), midbrain (tectum)
		55, M	21g	14d onset at 11d	Cerebellar syndrome, peripheral neuropathy Clinical improvement at 7 days	MRI: T2/FLAIR hyperintensities within the dentate, medulla (dorsal), pons (vestibular, abducens, inferior olivary nuclei), midbrain (tectum) and corpus callosum. f/u MRI at 15 days: residual signal changes within corpus callosum
		61, F	40.5g	27d onset at 24 d	Cerebellar syndrome Clinical improvement at 7 days	MRI: T2/FLAIR hyperintensities within the dentate and midbrain (tectum)
Kim et al., 2011 (41)		71, M	n/a	14d IV, 17d po	Encephalopathy – drowsiness, cerebellar syndrome Complete resolution at 3 months	CT: normal. MRI: T2/FLAIR hyperintensities within the dentate nuclei and splenium of the corpus callosum f/u MRI at 3 months: complete resolution
Lee et al., 2009 (42)	8	68, M	88g	44d	Cerebellar syndrome, peripheral neuropathy. Marked improvement at 15 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate and inferior colliculus; low ADC map f/u MRI at 4 days: complete resolution
		60, M	120g	60d	Cerebellar syndrome Marked improvement at 15 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate, inferior colliculus and medulla f/u MRI at 15 days: complete resolution
		64, F	100g	50d	Gait disturbance - ?ataxia Marked improvement at 15 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate, inferior colliculus and pons. f/u MRI at 15 days: complete resolution
		43, M	45g	30d	Cerebellar syndrome. Marked improvement at 15 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate, inferior colliculus and pons
		78, F	80g	40d	Gait disturbance - ?ataxia Marked improvement at 8 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate, inferior colliculus, corpus callosum and cerebral white matter
		76, F	100g	50d	Dysarthria - ?cerebellar Improvement at 13 day follow-up	MRI: MRI: T2/FLAIR hyperintensities within the dentate and inferior colliculus; low ADC map f/u MRI at 8 days: complete resolution
		61, M	120g	60d	Cerebellar syndrome and peripheral neuropathy Improvement at 18 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate and corpus callosum; low ADC map. f/u MRI at 6 days: residual signal changes within the corpus callosum
		47, M	100g	50d	Dysarthria - ?cerebellar Improvement at 15 day follow-up	MRI: T2/FLAIR hyperintensities within the dentate nucleus
Hammami et al., 2007 (39)	1	51, M	31.5g	21d	Cerebellar, vestibular, posterior column and pyramidal involvement	MRI: T2/FLAIR hyperintensities within the dentate nuclei, splenium of the corpus callosum and diffuse changes within the brainstem
Omotoso and Opadijo, 1997 (43)	1	48, M	n/a	3d	n/a	n/a
Park et al., 2011 (44) *	1	67, M	75g at onset (127.5g total)	~50d	Peripheral neuropathy, cerebellar syndrome, ?autonomic involvement Residual peripheral neuropathy at 6 months	MRI: T2/FLAIR hyperintensities within subcortical white matter and dentate nuclei; restricted diffusion within the subcortical white matter f/u MRI at 1 week: improvement in signal changes with no restricuted diffusion
Seok et al., 2003 (35)	1	74, F	90g	90d	MMSE 19/30, cerebellar syndrome, peripheral neuropathy and cogwheel rigidity; patient had co-existent vitamin B12 deficiency Remained on metronidazole for another three months after symptom onset Symptoms resolved within 4 months	MRI: T2/FLAIR hyperintensities within the subcortical white matter, anterior commissure, basal ganglia, dentate nuclei, splenium of the corpus callosum, inferior olivary nuclei and midbrain f/u MRI at 4 months: resolution of signal changes except within inferior olivary nuclei now demonstrating hypertrophy
Wienbren et al., 1985 (45)	1	43, F	18.5g IV, 10g (28.5g total)	12d, 10d	Encephalopathy and seizures Clinical resolution within 48 hours	CT: normal

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Table 4: Summary of case reports of metronidazole-induced seizures

Reference	n	Age, Sex	Cumulative Dose (g)	Duration (d)	Resolution	Imaging
Beloosesky et al., 2000 (46)	1	87, F	18g, 10.5g, 4.5g	12d, 7d, 3d	No recurrent seizures after d/c MTZ EEG #1: normal.EEG#2: diffuse slowing (delta/theta)	n/a
Frytak et al., 1978 (47)	3	52, F	52g	10d	'motor' seizure. EEG: no focal or epileptogenic activity. No recurrent seizure after d/c MTZ	CT (enhanced): unremarkable
		77, F	26g	10d	'motor' seizure. EEG: normal. No recurrent seizures	CT: normal
		75, F	42g	7d	'motor' seizure. EEG: normal. No recurrent seizures	CT: normal
George et al., 1982 (48)	1	61, M	20.7g IV	18d	Grand mal seizures with obtundation and death	n/a
Halloran et al., 1982 (49)	1	56, M	33.6g	16d	Resolution	n/a
Herreman et al., 1981 (50)	1	20, F	165g	68d	GTC seizures x 4 and neuropathy symptoms No recurrent seizures after d/c MTZ	n/a
Wienbren et al., 1985 (45)	1	43, F	18.5g IV, 10g (28.5g total)	12d, 10d	GTC seizures after MTZ discontinued; several within first 24 hrs despite tx with PHT. EEG: encephalopathy	CT: normal

Clinical Syndromes: 4. Optic Neuropathy

Optic neuropathy may be a rare complication of metronidazole treatment (summarized in Table 5;[15,51-53]). The link in the literature is not as clearly established. Patients have been described to develop subacute to chronic changes in visual acuity after prolonged treatment regimens of one to two years[15,51,52]. Marked improvement within days to weeks occurs immediately after discontinuation of metronidazole but full recovery was reported to take as long as a year (e.g.[51]). Putnam et al[53] reported a series of seven patients collectively by reviewing the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon). The reported symptoms consisted of abnormal color vision, scotomas and reduced visual acuity. One of the patients developed symptoms after only seven days of metronidazole therapy and in two of the reported patients the deficits were irreversible[53].

While at least one patient had a normal MRI[52] another had isolated splenium of the corpus callosum hyperintensities[15]. Cecil et al[51] describe a patient with a thickened splenium of the corpus callosum and marked signal changes within the basal ganglia and midbrain. Magnetic resonance spectroscopy (MRS) revealed elevated lactate peaks within the involved structures. Interestingly, there are no case reports of metronidazole-induced signal changes within the optic nerve.

Clinical Syndromes: 5. Autonomic Neuropathy

There is only one convincing case description of autonomic neuropathy secondary to metronidazole. This patient, a 15-year-old girl, developed severe painful peripheral sensorimotor neuropathy with absent sympathetic skin responses following a short course (reported as days of treatment) of metronidazole[54]. Extensive investigations were completed to rule out an alternative diagnosis or contributing cause. These included lumbar puncture, serum protein electrophoresis, rheumatoid factor, vitamin B_{12}, porphyrins, erythrocyte sedimentation rate (ESR), Lyme titer, antinuclear antibodies and lead, mercury and arsenic plasma levels. Symptoms were not immediately reversible upon discontinuation of metronidazole and multiple interim medications were required for the management of disabling neuropathic pain. Electrophysiological parameters and patient symptoms normalized at six months post cessation of metronidazole. Wienbren et al[45] suspected autonomic involvement in their patient who had urinary retention for 48 hours as well as concurrent seizures.

Clinical Syndromes: 4c. Peripheral Sensory or Sensorimotor Neuropathy

There are numerous reports of metronidazole-induced peripheral neuropathy in the literature and it remains the best-recognized neurologic side effect of metronidazole (selected cases are summarized in Table 5;[10,19,48,55-62]). In fact, many of the patients reported as having a cerebellar syndrome or encephalopathy, had co-existing neuropathic symptoms and/or findings (see Table 2 and 3). The neuropathy can be painful, severe and cause significant permanent disability (e.g.,[48]).

Although patients with coexisting central nervous system involvement have the typical radiological findings, patients with isolated peripheral sensory neuropathy do not appear to as demonstrated by one case report that included a normal MRI brain and cervical spine[62].

Metronidazole-induced neuropathy is characterized by a slowly progressive symmetric distal sensory neuropathy with primary small fiber involvement. Large fibers are affected subclinically in most cases. Routine electrodiagnostic studies may therefore be normal and quantitative sensory testing (QST), quantitative sudomotor autonomic reflex testing (QSART) and skin biopsy are more sensitive in this clinical setting. (e.g.,[62]). Gupta et al[19] described the only patient with a severe distal sensory neuropathy and an associated proximal motor neuropathy without resolution post discontinuation of metronidazole.

The proposed pathophysiology in metronidazole induced peripheral sensory neuropathy is axonal degeneration[60,63]and this may account for prolonged symptoms even after drug cessation. Human sural nerve biopsy studies have confirmed axonal degeneration in both myelinated and unmyelinated fibres[60]. Wallerian degeneration was confirmed in about 56% of fibers[63] while demyelination was relatively rare involving only 4%. The latter was thought to be a consequence of axonal pathology.

MR Imaging findings of Metronidazole Toxicity

The most common radiological abnormality induced by metronidazole consists of bilateral and symmetrical T2 and FLAIR hyperintensities within the dentate nuclei of the cerebellum on MR imaging (see Figure 1). There is no associated mass effect or enhancement but, occasionally, there is a subtle T1

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Table 5: Summary of case reports of optic, autonomic and selected cases of peripheral neuropathy secondary to metronidazole treatment

Reference	n	Age, Sex	Cumulative Dose (g)	Duration (d)	Resolution	Imaging
Optic Neuropathy						
Cecil et al., 2002 (51)	1	17, M	n/a	n/a	Slight improvement in visual acuity at 1 month, marked improvement at 3 months and full resolution at 1 year. (other symptoms: cerebella syndrome and peripheral neuropathy)	MRI: T2/FLAIR hyperintensities within the corpus callosum (associated with thickening), midbrain and basal ganglia. MRS: elevated lactate peaks (basal ganglia and splenium of the corpus callosum)
De Bleecker et al., 2005 (15)	1	20, M	1095g	~730d	Improvement within 2 weeks of d/c Resolution within 14 months	MRI: T2/FLAIR signal hyperintensities within the splenium of the corpus callosum
McGrath et al., 2007 (52)	1	67, F	~360g	~300d	Improvement within 4 d of d/c Resolution of optic neuropathy	MRI: normal
Putnam et al., 1991 (53)	7	26-53yo; 4W, 5M	n/a	7 to 365d	Two out of seven patients had residual deficits in vision; peripheral neuropathy in two	n/a
Autonomic Neuropathy						
Hobson-Webb et al., 2006 (54)	1	15, F	n/a	Short course	Dramatic improvement 3 mo later Complete resolution by 6 mo	MRI/MRA: normal
Wienbren et al., 1985 (45)	1	43, F	18.5g IV, 10g (28.5g total)	12d, 10d	Urinary retention x 48 hours – autonomic involvement suspected; ?other cause GTC seizures after MTZ discontinued	CT: normal
Peripheral Neuropathy						
Bradley et al., 1977 (55)	1	33, M	~336gg	9mo	Sensory symptoms started at 8 weeks EMG – distal, primarily sensory peripheral neuropathy	n/a
Coxon and Pallis, 1976 (56)	2	60, F	30.6g	50d	Improvement of symptoms at 1 month	n/a
		40, M	114g	63d	No improvement at 1 month follow-up	n/a
George et al., 1982 (48)	2	43, M	27.5g iv + 101.3g po	58d	-	n/a
		48, M	4.1g iv + 15.8g po	9d	Severe sensory neuropathy	n/a
Gupta et al., 2000 (57)	1	25, M	18g	15d	-	n/a
Gupta et al., 2003 (13)	1	50, M	200g	84d	Other features: cerebellar syndrome, encephalopathy	CT: hypodensities within the cerebellum
Kusumi et al., 1980 (10)	1	45, F	84g	28d	-	n/a
Ramsay, 1968 (58)	1	43, M	135g	113d	-	n/a
Sarma and Kamath, 2005 (59)	1	45, F	3.6g	3d	Improvement of symptoms upon discontinuation	n/a
Takeuchi et al., 1988 (60)	1	67, M	101.25g	-	-	n/a
Tan et al., 2011 (61)	1	53, M	146g	88d	Length-dependent painful neuropthy	n/a
Zivkovic et al., 2001 (62)	4	52, M	180g	90d	Symptom onset at 10 weeks	n/a
		34, F	n/a	120d (intermittent)	Symptoms resolved post discontinuation	MRI brain and C-spine: unremarkable
		55, M	3650g	3650d	-	n/a
		51, F	(topical)	270d	-	n/a

hypointensity noted (e.g.,[20]). This finding of involvement of the cerebellar dentate nuclei, is almost pathognomonic, although a small, less likely differential can be invoked (eg, Wernicke's encephalopathy, Friedreich's ataxia, CADASIL, cerebrotendinous xanthomatosis). Typically, patients with these changes on MR imaging show a cerebellar syndrome, with or without a peripheral neuropathy.

In patients with metronidazole-induced encephalopathy, involvement of the splenium of the corpus callosum is also frequently found either in isolation or in association with dentate nuclei signal abnormalities (e.g.,[31,34,35]). Other sites of involvement, include midbrain, pons, medulla, subcortical white matter, basal ganglia, anterior commissure and middle cerebellar peduncle[31,34,35].

Generally, MR signal abnormalities are fully reversible with drug discontinuation and are therefore attributed to axonal swelling (i.e. increased water content) instead of a demyelinating process[35]. Alternatively, Ahmed et al[11] proposed that these changes may represent vascular spasm and transient reversible ischemia.

Many case reports of MRI findings describe high diffusion weighted imaging (DWI) signal associated with low apparent diffusion coefficient (ADC) values suggesting cytotoxic edema within the corpus callosum, basal ganglia, brainstem and subcortical white matter[35,40]. Dentate nuclei, however, typically demonstrate high DWI signal associated with high ADC values indicative of vasogenic edema[40,42]. Cecil et al[51] reported proton MRS findings in a patient with metronidazole toxicity demonstrating a high lactate peak.

Animal Studies of Metronidazole Toxicity

Reports of metronidazole-induced neurotoxicity in cats and dogs include a cerebellar syndrome, seizures, changes in level of consciousness and nystagmus[64-67]. It is not clear whether the doses are comparable to those used in humans. Scharer et al[67] demonstrated clear loss of Purkinje cells in dogs exposed to metronidazole - clinical recovery would therefore be unexpected.

Experimental models aimed at studying metronidazole toxicity are not current. Animal studies have clearly shown that ^{14}C-metronidazole crosses the blood-brain barrier and accumulates within the brain particularly within the hippocampus, olfactory bulb and cerebellum[68]. Moreover, autoradiographic studies of the hippocampus and cerebellum showed that these structures retain activity for longer periods of time[68] perhaps accounting for the recognized clinical and radiological toxicity of metronidazole within the cerebellum noted within the human literature.

Administration of high doses of metronidazole to rats (800 mg/kg/day over six weeks) has been shown to produce symmetrical lesions within the vestibular and cochlear nuclei as well as cerebellar nuclei[69]. The involved sites were strikingly similar to those found in Wernicke's encephalopathy. However, the doses were approximately 25-fold higher than the maximum

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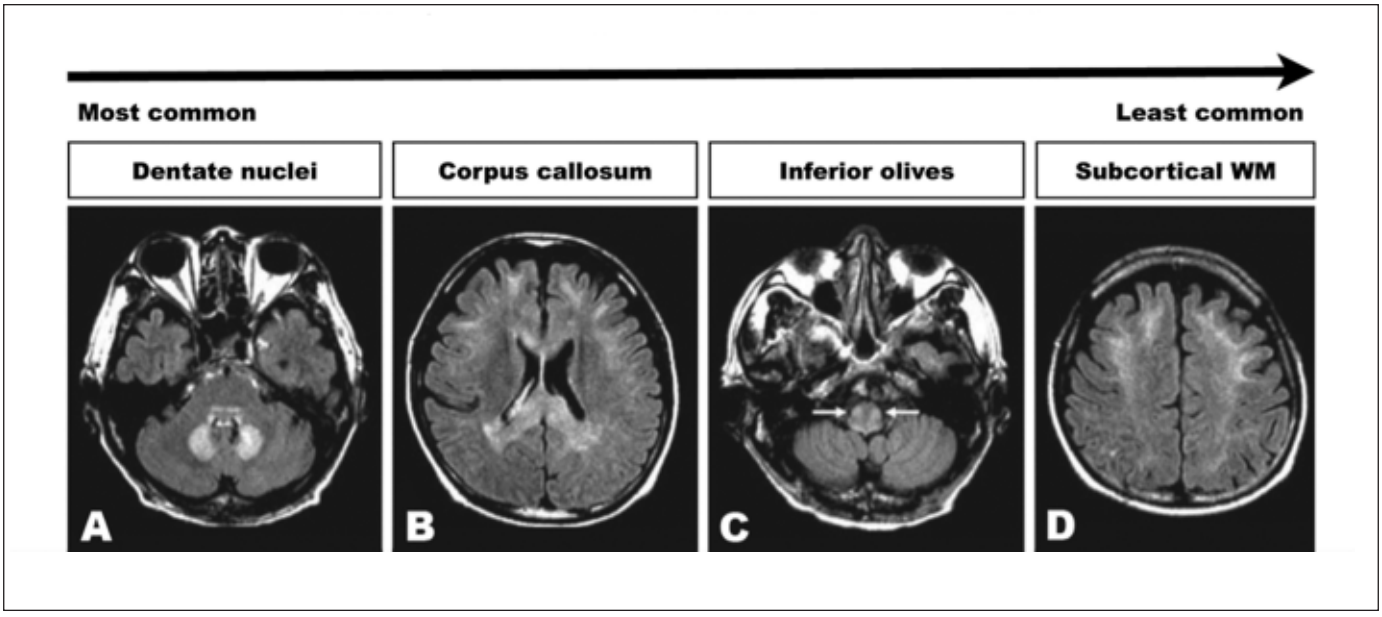

Figure: *Summary of metronidazole-induced MRI features from most common (left, A) to least common (right, D). Metronidazole-induced MRI FLAIR hyperintensities are found within the cerebellar dentate nuclei (A), corpus callosum (splenium) (B), inferior olives (C) and subcortical white matter (WD) (D). (Adapted from Kim et al. (40) with permission).*

recommended dose in humans. Furthermore, metabolism of metronidazole, at least in mice and rats, has been shown to be different than in humans[70] and animal studies need to be extrapolated with caution. Administration of metronidazole to rats at doses comparable to humans, did not result in cerebellar or brainstem lesions[55]. Radioactively-labeled metronidazole was found to bind to RNA and thus neurotoxicity may be related to inhibition of protein synthesis by metronidazole or one of its metabolites[55].

Pathophysiology

The pathophysiology underlying metronidazole neurotoxicity remains elusive although several possible mechanisms have been proposed. It is not known whether metronidazole itself is neurotoxic or whether the culprit is one of its metabolites.

Metronidazole has been shown to bind to RNA and proposed to inhibit protein synthesis thereby presumably leading to axonal degeneration[55]. Others have postulated that metronidazole leads to free radical formation[71].

Alston[72] hypothesized that neurotoxicity may be related to metronidazole's structural similarity to the thiazole precursor of thiamine. Gut flora possessing thiaminase activity may be involved in the conversion of metronidazole to a thiamine antagonist. Whether the neurotoxic side effects could be mitigated by supplemental thiamine administration has never been explored although the similarity in MR changes between Wernicke's encephalopathy and metronidazole induced encephalopathy is intriguing.

Recently, similar neurotoxicity was described in a related 5-nitro-imidazole derivative, ornidazole[73]. Symmetric and reversible T2/FLAIR hyperintensities within the dentate nuclei were also found. Interestingly, another related compound – tonidazole – did not cause neurotoxicity in a patient who previously developed a metronidazole-induced cerebellar syndrome[24]. However, toxic doses of tonidazole in another patient who was self-medicating, resulted in side effects and radiological findings identical to metronidazole[74]. Thus, neurotoxicity of 5-nitro-imidazole derivatives likely shares the same pathophysiology.

Metronidazole levels are not routinely measured in patients with neurologic complications. While some patients clearly have toxic metronidazole levels (e.g.,[16,18,21]) others do not (e.g.,[29]). Although there are no consistent patient-related factors, some have suggested that advanced age as well as renal and hepatic dysfunction may confer a higher risk of developing metronidazole-related side effects.

Alston[75] studied metronidazole metabolism in the elderly (over 70 years-old) and healthy controls, concluding that in the elderly the smaller volume of distribution, declining renal function and reduced red cell binding of metronidazole results in higher serum levels potentially leading to neurotoxicity. However, similar experiments[76] found no difference in metabolism of metronidazole in the elderly (studied patients 86 +/- 6 years-old) and recommended no changes to dosing.

Hepatic dysfunction leads to impaired hepatic oxidation and, therefore, reduced metronidazole elimination[30]. Similarly, severe renal failure increases metronidazole's half-life from 9.2 hours to 28 hours[77]. Therefore, prudent use and/or dose adjustment in these clinical scenarios would seem to be warranted.

Kuriyama et al[78] conducted a systematic review to ascertain patient and medication-related features associated with metronidazole toxicity. Based on inclusion criteria, 64 patients were included in the analysis. The most common presentation of metronidazole neurotoxicity is a cerebellar syndrome (present in 77% of patients) followed by encephalopathy (33%). Although side effects were more commonly associated with chronic

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treatment regimens, 26% of patients developed symptoms in less than a week. The authors concluded that dose and duration of treatment are ultimately not correlated with central nervous system toxicity.

Discussion and Conclusions

Despite its widespread use in clinical practice, the neurotoxicity of metronidazole continues to be under recognized. In fact, patients are not usually informed about the potential neurologic complications when being started on this antimicrobial. Fortunately, serious side effects continue to be relatively rare and often fully reversible before a diagnosis is made. These side effects may also be less obvious in complicated patients due to polypharmacy or coexisting conditions predisposing them to neuropathy, seizures or even ataxia.

More recently, there has been a surge of case reports on its neurotoxic effects likely attributable to more widespread and chronic use of metronidazole (i.e. more affected patients) as well as routine MRI imaging demonstrating the typical T2 and FLAIR signal changes (i.e. identification of metronidazole as an offending neurotoxic agent).

Recognition of the neurotoxic effects of metronidazole cannot be overemphasized, as prompt discontinuation is associated with a favorable long-term prognosis. Moreover, heightened index of suspicion about neurological syndromes produced by metronidazole may decrease the need for extensive investigations. When metronidazole is suspected to be the cause of neurological symptoms, however, it should remain a diagnosis of exclusion to ensure that no other reversible cause is missed particularly in the absence of characteristic MRI findings.

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