

# Metronidazole induced encephalopathy: case report and discussion on the differential diagnoses, in particular, Wernicke's encephalopathy

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## ABSTRACT

Metronidazole induced encephalopathy is a rare central nervous system toxicity, which may be completely reversible with prompt cessation of metronidazole usage. We present a case of metronidazole induced encephalopathy in a 59-year-old man with a history of Whipple's procedure for pancreatic neuroendocrine tumour. The characteristic magnetic resonance imaging features of metronidazole induced encephalopathy and its main differential diagnosis, Wernicke's encephalopathy, are discussed.

## CASE REPORT

### CASE REPORT

A 59-year-old man presented with sudden onset of slurred speech, difficulty in swallowing, and right sided weakness. He had significant recent surgical history of Whipple's procedure for a pancreatic uncinete neuroendocrine tumour. The operation was complicated by intra-abdominal infection, for which the patient was treated with metronidazole and ciprofloxacin for the past six weeks.

On examination, he was found to have moderate dysarthria, nystagmus, upper limb dysmetria, and wide-based ataxic gait. No clinical ophthalmoplegia or encephalopathy was detected.

No acute intracranial abnormality was detected on CT brain. An abbreviated magnetic resonance imaging (MRI) brain protocol tailored for stroke evaluation was performed as this was the main clinical impression. The MRI brain (Figure 1) showed bilateral symmetrical T2-weighted hyperintensities in the dentate nuclei (A, long arrows), dorsal medulla (A, short

arrows), vestibular nuclei (B, long arrows), superior olivary nuclei (B, short arrows), abducens nuclei (B, arrowheads), and tectum (C, arrowheads). The medial thalami were unremarkable (D). DWI hyperintensities were demonstrated in bilateral dentate nuclei (E) and superior olivary nuclei (F). No corresponding low ADC signal was seen at these regions to suggest restricted diffusion. The diagnosis of metronidazole induced encephalopathy (MIE) was made from the neuroimaging findings and the history of prolonged metronidazole use. The offending drug was stopped and the patient's neurological deficit improved progressively.

### DISCUSSION

#### Etiology & Demographics:

Metronidazole is a widely used and well-tolerated anti-anaerobic and anti-protozoal agent. MIE is a rare central nervous system toxicity that was first described by Ahmed et al in 1995 [1] and its incidence and underlying mechanism remain uncertain. Some postulated that the toxicity is due to

binding of metronidazole or its metabolites to the neuronal RNA which results in neural dysfunction [2], while others proposed that the radicals formed in the reaction between catecholamine neurotransmitters (such as norepinephrine and dopamine) and metronidazole are the underlying cause for neuronal damage [3].

There are no established risk factors for MIE. Sørensen et al have reported that liver disease was the most common pre-existing condition in patients with MIE (15%) [4]. For our patient, his comorbidities were diabetes, hypertension, hyperlipidemia, and pancreatic neuroendocrine tumour. Kim et al have shown that the affected patients usually have a significant mean cumulative dose of 58.1 g (range 21 – 135 g) for a prolonged duration of 38.7 days (range 14 – 90 days) [5]. Our patient was administered a cumulative dosage of 53 g of metronidazole over 6 weeks, before the diagnosis of MIE.

#### Clinical & Imaging Findings:

Majority of patients with MIE present with cerebellar dysfunction, followed by altered mental status and seizure. The most common cerebellar signs are dysarthria, ataxia, and dysmetria [6].

Several characteristic radiological features of MIE have been reported in literature [5]. Bilateral symmetrical T2-weighted hyperintense lesions can be seen in cerebellar dentate nuclei, midbrain, dorsal pons, dorsal medulla, and corpus callosum, but typically involve the dentate nuclei. If the dorsal pons is involved, the lesions tend to be found at the abducens nuclei, vestibular nuclei, and superior olivary nuclei. Involvement of the corpus callosum tends to be at the splenium [5]. The location of T2-weighted hyperintense lesions in our patient are consistent with the reported distribution of the most frequently affected regions.

#### Treatment & Prognosis:

Most patients with MIE have good prognosis after discontinuation of metronidazole. Majority have either improvement of their symptoms (29%) or complete recovery (65%). Minority experience permanent cognitive impairment. Patients with altered mental status or seizures are more likely to have complete recovery than those with cerebellar dysfunction [6]. Our patient had mild residual dysmetria at his last neurological assessment. On the other hand, continuation of metronidazole therapy in patients with MIE can potentially lead to irreversible adverse outcome. Progressive encephalopathy leading to mortality has been reported occasionally [7,8].

#### Differential Diagnoses:

The main differential diagnosis to consider is Wernicke's encephalopathy, which is a condition caused by thiamine deficiency. It affects alcoholics and non-alcoholics, and can present with clinical signs/symptoms and radiological findings similar to MIE. The clinical presentation has been described by the classical triad of encephalopathy, ataxia, and ophthalmoplegia. Typical imaging findings of Wernicke's

encephalopathy are bilateral symmetrical T2-weighted hyperintensities in mammillary bodies, medial thalami, and periaqueductal grey matter [9], which are specific and not seen in MIE (Figure 2). However, atypical imaging findings similar to MIE can be present in non-alcoholic patients. They include T2-weighted signal abnormalities in dentate nuclei, cerebellar vermis, cranial nerve nuclei, and splenium of corpus callosum [9,10].

Therefore the differentiation between MIE and non-alcoholic Wernicke's encephalopathy can be difficult, especially so in patients with history of gastrointestinal surgery and systemic infection as they are concurrently at risk of thiamine deficiency and receiving metronidazole therapy. Fortunately, the atypical findings seen in non-alcoholic Wernicke's encephalopathy are usually associated with the more specific typical findings [11,12]. In our patient, although the differential diagnosis of Wernicke's encephalopathy was considered, the absence of ophthalmoplegia or clinical encephalopathy was noteworthy. In addition, the absence of typical mammillary bodies, medial thalami, and periaqueductal grey matter involvement was not consistent with Wernicke's encephalopathy.

Methyl bromide intoxication is a rare type of toxic encephalopathy with imaging features closely resembling those of MIE: bilateral symmetrical T2-weighted hyperintensities in cerebellar dentate nuclei, dorsal pons, dorsal medulla, splenium of corpus callosum, and cranial nerve nuclei [13]. However, it is unlikely in our case without any history of exposure to fumigant gas or relevant industrial exposure. Demyelinating disease such as multiple sclerosis can demonstrate lesions in the brain stem and cerebellum. However, the lesions are usually not symmetrical and do not selectively affect the cranial nerve nuclei. For multiple sclerosis, periventricular, cortical, juxtacortical, infratentorial, and spinal cord T2-weighted hyperintense lesions can be seen, with active lesions showing restricted diffusion and contrast enhancement [14]. There can be multiple clinical attacks with various acute presentations depending on the location of active lesions. Multifocal infarctions are usually randomly distributed in the brain parenchyma with evidence of restricted diffusion, not consistent with the radiological findings of our case.

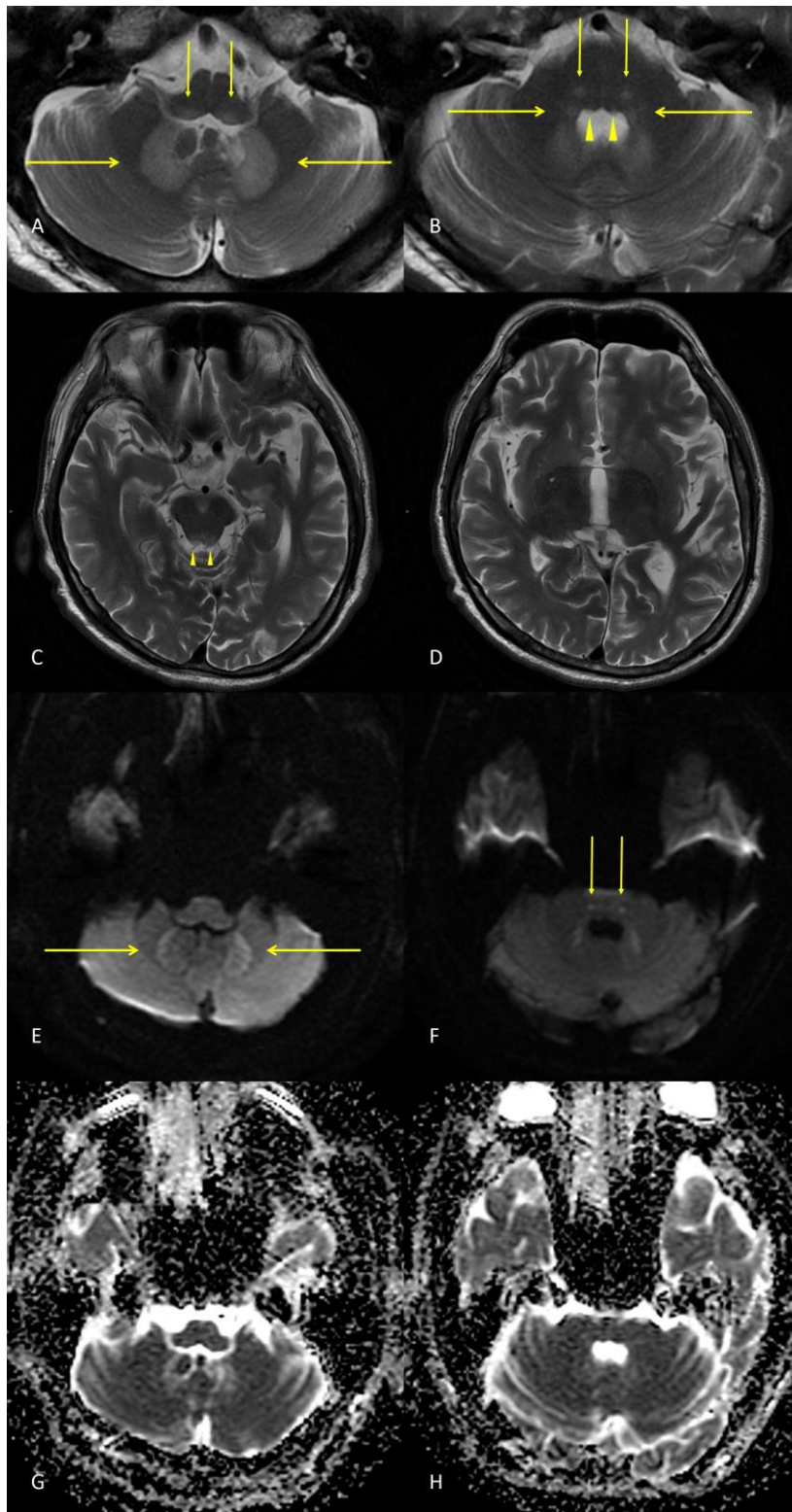
#### TEACHING POINT

Metronidazole is a commonly used antibiotic and patients with protracted clinical history may be administered high cumulative doses. Metronidazole induced encephalopathy is a rare but important sub-acute complication that has characteristic MRI features. Bilateral symmetrical T2-weighted hyperintense lesions are typically seen in cerebellar dentate nuclei, midbrain, dorsal pons, dorsal medulla, and splenium of corpus callosum. Early recognition of these imaging findings with prompt cessation of the medication improves prognosis and prevents irreversible neurological damage. The main differential consideration is Wernicke's encephalopathy, especially non-alcoholic Wernicke's encephalopathy with atypical findings.

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## FIGURES



**Figure 1:** 59-year-old man with metronidazole induced encephalopathy.

**FINDINGS:** MRI brain shows bilateral symmetrical T2-weighted hyperintensities in the dentate nuclei (A, long arrows), dorsal medulla (A, short arrows), vestibular nuclei (B, long arrows), superior olivary nuclei (B, short arrows), abducens nuclei (B, arrowheads), and tectum (C). The medial thalami are unremarkable (D). DWI hyperintensities are demonstrated in bilateral dentate nuclei (E) and superior olivary nuclei (F). No corresponding low ADC signal is seen at these regions to suggest restricted diffusion (G, H).

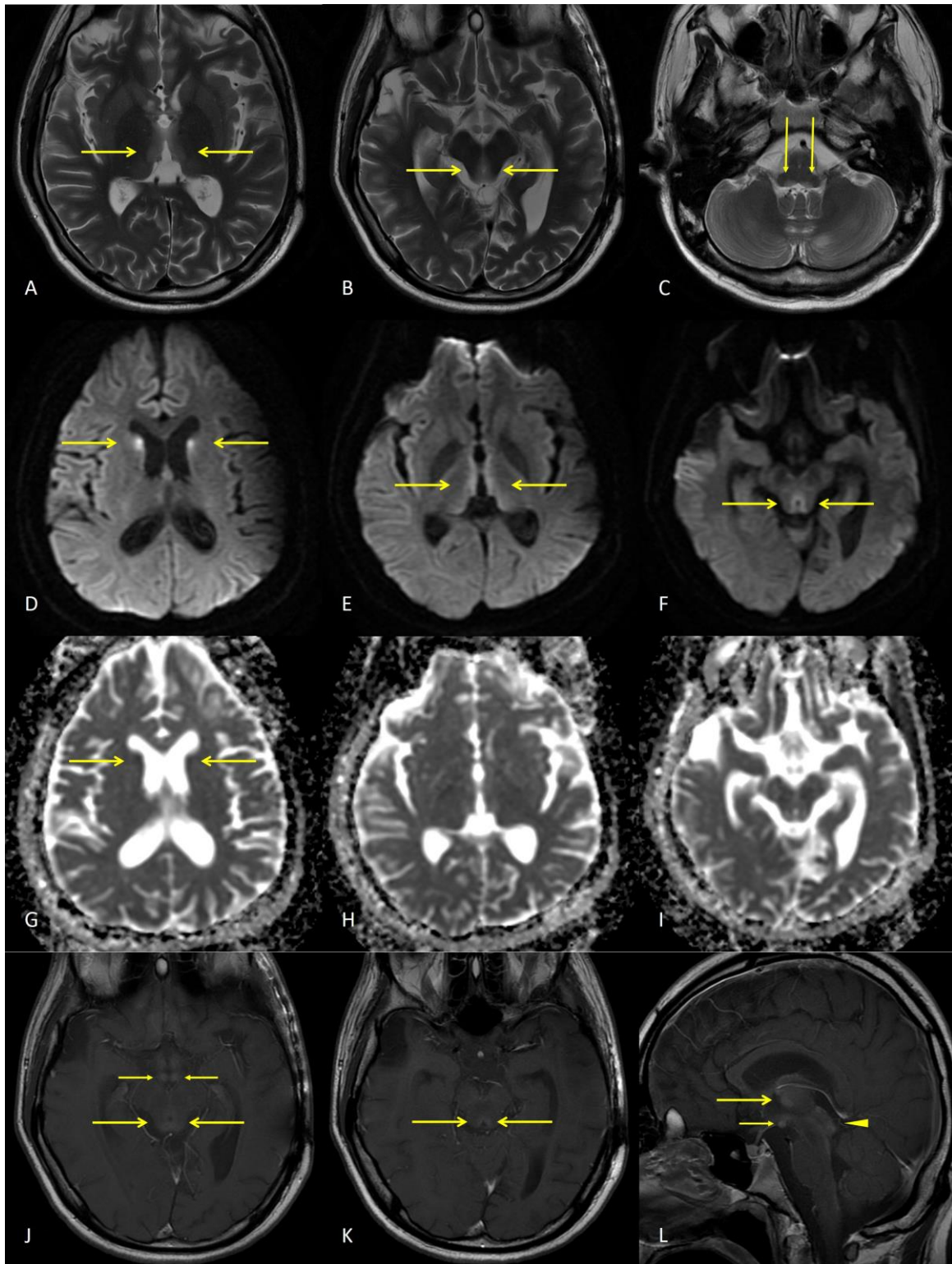
**TECHNIQUE:** GE Signa HDxt MRI scanner. Magnetic strength 3.0 Tesla.

A-D: Axial T2-weighted, TR 5300 ms, TE 90 ms, slice thickness 5 mm.

E, F: Axial DWI, TR 4000 ms, TE 88 ms, slice thickness 5 mm.

G, H: Axial ADC, TR 4000 ms, TE 88 ms, slice thickness 5 mm.





**Figure 2:** 25-year-old man with Wernicke's encephalopathy

**FINDINGS:** The MRI brain shows bilateral symmetrical T2-weighted hyperintensities in medial thalami (A), periaqueductal grey matter (B), and dorsal medulla (C). DWI hyperintensities are demonstrated in caudate nuclei (D), medial thalami (E), and periaqueductal grey matter (F, characteristic "Ω" shape). Corresponding low ADC signal is present at caudate nuclei, in keeping with restricted diffusion (G), while no corresponding low ADC signal is seen in medial thalami or periaqueductal grey matter (H, I). Enhancement in periaqueductal grey matter (J and K, long arrows), mammillary bodies (J and L, short arrows), medial thalami (L, long arrow), and tectum (L, arrowhead) is noted after administration of intravenous contrast.

**TECHNIQUE:** GE Signa HDxt MRI scanner. Magnetic strength 3.0 Tesla.

A-C: Axial T2-weighted, TR 5100 ms, TE 98 ms, slice thickness 5 mm.

D-F: Axial DWI, TR 3750 ms, TE 88 ms, slice thickness 5 mm.

G-I: Axial ADC, TR 3750 ms, TE 88 ms, slice thickness 5 mm.

J, K: Axial contrast enhanced T1-weighted, TR 640 ms, TE 18 ms, slice thickness 5 mm.

L: Sagittal contrast enhanced T1-weighted, TR 600 ms, TE 18 ms, slice thickness 5 mm.

<b>Etiology</b>	The exact etiology remains unknown. Some postulations: <ul style="list-style-type: none"> <li>• Binding of metronidazole or its metabolites to the neuronal RNA results in neural dysfunction.</li> <li>• Radicals formed in the reaction between catecholamine neurotransmitters (such as norepinephrine and dopamine) and metronidazole cause neuronal damage.</li> </ul>
<b>Incidence</b>	Rare, unknown
<b>Gender ratio</b>	Unknown
<b>Age predilection</b>	Unknown
<b>Risk factors</b>	The affected patients usually have a significant mean cumulative dose of 58.1 g (range 21 – 135 g) for a prolonged duration of 38.7 days (range 14 – 90 days).
<b>Treatment</b>	Prompt cessation of metronidazole administration
<b>Prognosis</b>	Most have good prognosis after discontinuation of metronidazole. <ul style="list-style-type: none"> <li>• Majority have either improvement of their symptoms (29%) or complete recovery (65%). Minority experience permanent cognitive impairment.</li> <li>• Patients with altered mental status or seizures are more likely to have complete recovery than those with cerebellar dysfunction.</li> </ul>
<b>Findings on imaging</b>	Characteristic radiological features: <ul style="list-style-type: none"> <li>• Bilateral symmetrical T2-weighted hyperintense lesions can be seen in cerebellar dentate nuclei, midbrain, dorsal pons, dorsal medulla, and corpus callosum, but typically involve the dentate nuclei.</li> <li>• If the dorsal pons is involved, the lesions tend to be found at the abducens nuclei, vestibular nuclei, and superior olivary nuclei.</li> <li>• Involvement of the corpus callosum tends to be at the splenium.</li> </ul>

**Table 1:** Summary table for metronidazole induced encephalopathy

	<b>Imaging Features</b>	<b>Clinical Presentation</b>
<b>Metronidazole induced encephalopathy (MIE)</b>	Characteristic radiological features: <ul style="list-style-type: none"> <li>• Bilateral symmetrical T2-weighted hyperintense lesions can be seen in cerebellar dentate nuclei, midbrain, dorsal pons, dorsal medulla, and corpus callosum, but typically involve the dentate nuclei.</li> <li>• If the dorsal pons is involved, the lesions tend to be found at the abducens nuclei, vestibular nuclei, and superior olivary nuclei.</li> <li>• Involvement of the corpus callosum tends to be at the splenium.</li> </ul>	Majority present with cerebellar dysfunction, followed by altered mental status and seizure. The most common cerebellar signs are dysarthria, ataxia, and dysmetria.
<b>Wernicke's encephalopathy</b>	Typical imaging findings: bilateral symmetrical T2-weighted hyperintensities in mammillary bodies, medial thalami, and periaqueductal grey matter, which are specific and not seen in MIE. <ul style="list-style-type: none"> <li>• However, atypical imaging findings similar to MIE can be present in non-alcoholic patients: lesions in dentate nuclei, cerebellar vermis, cranial nerve nuclei, and splenium of corpus callosum.</li> <li>• Fortunately, the atypical findings in non-alcoholic Wernicke's encephalopathy are usually associated with the more specific typical findings.</li> </ul>	Caused by thiamine deficiency. It can affect both alcoholics and non-alcoholics. Classical clinical triad of encephalopathy, ataxia, and ophthalmoplegia.
<b>Methyl bromide intoxication</b>	Close resemblance to MIE: bilateral symmetrical T2-weighted hyperintensities in cerebellar dentate nuclei, dorsal pons, dorsal medulla, splenium of corpus callosum, and cranial nerve nuclei.	Prior exposure to fumigant gas or relevant industrial exposure.
<b>Demyelinating disease such as multiple sclerosis</b>	Lesions are usually not symmetrical and do not selectively affect the cranial nerve nuclei. For multiple sclerosis, periventricular, cortical, juxtacortical, infratentorial, and spinal cord T2-weighted hyperintense lesions can be demonstrated, with active lesions showing restricted diffusion and contrast enhancement.	Multiple attacks with various acute presentations depending on the location of active lesions.
<b>Multifocal infarctions</b>	Usually randomly distributed in the brain parenchyma with evidence of restricted diffusion	Acute stroke with variable neurological deficiency

**Table 2:** Differential diagnosis table for metronidazole induced encephalopathy

## ABBREVIATIONS

ADC = Apparent diffusion coefficient  
DWI = Diffusion weighted imaging  
MIE = Metronidazole induced encephalopathy  
MRI = Magnetic resonance imaging

## KEYWORDS

Metronidazole induced encephalopathy; Wernicke's encephalopathy; cerebellar dysfunction; dentate nuclei; magnetic resonance imaging

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