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An Unusual Case of Metronidazole Induced Encephalopathy

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Abstract: ***Introduction: Metronidazoleis a fairly well tolerated drug, however it can produce several adverse neurologic effects. The incidence of metronidazole induced encephalopathy (MIE) is uncommon. Neuroimaging manifestations of metronidazole toxicity mainly includes lesions of the Cerebellum, brain stem and corpus callosum. The first case of MIE was published way back in 1977. Since then few cases have been reported and awareness of this condition among clinicians has substantially increased, especially in the last decade. Maximum cases presented with cerebellar dysfunction followed by altered mental status and seizures. Among cerebellar dysfunction dysarthria, ataxia, dysmetria and nystagmus were most common. Altered mental status is generally a part of the encephalopathy. Withholding metronidazole as early as possible along with supportive therapy is the only proven measure. Case Report: A 77 years old male presented to our hospital with chief complaints of generalized weakness since 15 days, slurring of speech since 2 days and disoriented since the morning of admission. Patient is a case of Amoebic Liver Abscess diagnosed 10 weeks back. Patient was started on Inj Metronidazole 2.4 grams / day for the first 14 days which was then converted to Tab Metronidazole 2.4 grams / day which was continued till admission. On examination patient appeared drowsy and disoriented. Dysarthria was present. Nystagmus was present. MRI Brain showed Bilaterally Symmetrical Hyperintensities in Red Nucleus and dentate nucleus. Tab Metronidazole was Stopped and within 48 hours of stopping the drug patient sensorium improved. Conclusion: Neurotoxicity is an important but rare adverse effect of Metronidazole. Our patient developed encephalopathy following the initiation of Metronidazole at High Dose and showed complete improvement after discontinuation. This temporal relationship supports the diagnosis of Metronidazole Induced Encephalopathy.***

Keywords: MIE (Metronidazole induced encephalopathy), Dentate nucleus, Neurotoxicity, Dysarthria, Amoebic liver abscess.

1. Introduction

Metronidazole is a synthetic 5 - nitroimidazole that exhibits amoebicidal activity and commonly used in the treatment of several protozoal and anaerobic infections. Its main indications are Amoebiasis, Trichomonal infection, Helicobacter Pylori infection and Clostridium difficile associated Diarrhoea. Additionally, it is often used in Crohn's disease and Hepatic abscess. Metronidazole is a fairly well tolerated drug, however it can produce several adverse neurologic effects including peripheral neuropathy, Cerebellopathy, Encephalopathy, Visual impairment, Vestibulo - toxicity, Cochlear - toxicity, Ataxia, dysarthria and seizuresin both long term and short term use. The incidence of metronidazole induced encephalopathy (MIE) is uncommon. Neuroimaging manifestations of metronidazole toxicity mainly includes lesions of the Cerebellum, brain stem and corpus callosum. On MRI Reversible high signal intensity of the cerebellar dentate nuclei has often been reported in several cerebellopathycases. If present, characteristic imaging findings and partial or complete normalization of these findings after discontinuation of the drug 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. Since then few cases have been reported and awareness of this condition among clinicians has substantially increased, especially in the last decade.

Epidemiology - Maximum cases of Neuro - toxicity from metronidazole are reported from United States and Korea. There have been few case reports worldwide including India, Japan, Australia, Canada, United Kingdom, Belgium, Chile, Germany, Israel, Netherlands, Nigeria, Taiwan, Tunisia, and Turkey. The condition can develop within 1 to 90 days of initiation of treatment and average cumulative dose is 93.4g (range 0.25 - 1095 grams). There is no sex predisposition and majority of reports describe adult cases, though there have been a few paediatric cases reported worldwide.

Clinical Features - Out of the majority of published case reports of metronidazole toxicity to the Central nervous system, maximum cases presented with cerebellar dysfunction followed by altered mental status and seizures. Among cerebellar dysfunction dysarthria, ataxia, dysmetria and nystagmus were most common findings on examination. Altered mental status is generally a part of the encephalopathy. Metronidazole toxicity can also present as extrapyramidal manifestations. There are few reported cases of chorea and myoclonus as presenting symptom. There are also reported cases of pure sensorineural hearing loss as a presenting symptom.

Mechanisms of Toxicity - The mechanism of neurotoxicity by metronidazole still remains unclear, though several hypothesis have been proposed. Metronidazole concentration is fairly high in the extracellular space of brain which can contribute to its toxicity. Intermediate metabolites of metronidazole may bind to RNA or DNA of the neuronal cells. 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. Vascular spasms may also produce reversible localized ischemia as seen in cases of "true" diffusion restriction. Double peak of lactate on Magnetic Resonance Spectroscopy (MRS) as reported in some cases point to a mitochondrial insult as a plausible pathogenesis. Gamma Amino butyric acid receptor modulation within the cerebellum and vestibular systems has been studied in dogs as a model for metronidazole induced toxicity. Experimental studies have also been performed which revealed lesions mainly of brain stem and cerebellum. However pathologic changes in basal ganglia, corpus callosum or white matter have not been reported. Additionally, researchers have also reported similar clinical features including Encephaloneuropathy with other 5 - nitroimidazoles like tinidazole.

Differential diagnosis - Other Encephalopathies with bilateral T2 hyperintensities of the dentate nuclei are methyl bromide intoxication, Enteroviral encephalomyelitis and Maple syrup urine disease. T2 hyperintense lesions of the splenium may be observed in various demyelinating disorders (such as Marchiafava - Bignami disease, Osmotic myelinolysis). These lesions may be transiently seen in disorders like epilepsy (overdose or abrupt withdrawal), acute infectious encephalitis, demyelinating lesions including acute disseminated encephalomyelitis or systemic lupus erythematosus, stroke, hypertensive encephalopathy, preeclampsia, hypoglycaemia, hyponatraemia, high altitudinal oedema and acute toxic encephalopathy (methotrexate and 5 - fluorouracil). Diffusion restriction with low ADC has been noted in metabolic encephalopathies like Wernicke's encephalopathy and Maple syrup urine disease and rarely in demyelinating disorders like Canavan disease. Clinical scenario, laboratory and other investigations can easily differentiate metronidazole toxicity from these disorders in 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, though there is a paucity of data on the same.

Management - Withholding metronidazole as early as possible along with supportive therapy is the only proven measure. Alternative therapy may be started for the initial infection depending upon the culture and antibiotic sensitivity report from the respective specimen. In cases of hepatic encephalopathy metronidazole should be replaced with oral vancomycin, paromomycin, oral quinolones, or rifaximin. 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. 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.

2. Case Report

A 77 years old male presented to our Hospital with chief complaints of generalized weakness since15 days, slurring of speech since 2 days and disoriented since the morning of admission. Patient is a case of Amoebic Liver Abscess diagnosed 10 weeks back (230 cc puss on USG) status post needle aspiration of 60cc puss from segment VI of liver. Patient was started on Inj Metronidazole 2.4 grams / day for the first 14 days which was then converted to Tab Metronidazole 2.4 grams / day which was continued till admission. On examination patient appeared drowsy and disoriented to time, place and person. His GCS was E_3 V_2 M_4 and Four Score E_2 M_2 B_4 R_4. Pupils were bilaterally 2 – 3 mm, equally reactive to light. Planters were flexor bilaterally. Deep Tendon Reflexes were normal. No neck rigidity or other meningeal signs. Dysarthria was present. Tone was normal throughout and there was no abnormal movement. Nystagmus was present. On Per Abdomen Examination liver was palpable 4 cm below the Right Subcoastal margin at the Mid - clavicular Line with sharp margin, smooth surface and firm consistency. On USG abdomen 118 cc hepatic abscess localized in Segment VI. MRI Brain Plain showed Bilaterally Symmetrical Hyperintensities in Red Nucleus and dentate nucleus. Based on the History of Long - term High dose Metronidazole ingestion and clinical features and imaging It was Diagnosed with **Metronidazole Induced Encephalopathy**. During his stay in hospital patient was never Oliguric.

Table 1: Laboratory Findings During Hospital Stay

	Day 1	Day 3	Day 5
Hb (gm/dl)	12.8	13.7	13.7
TLC (* 10^3/microlitre)	7.7	9.1	8.9
Platelets (* 10^3/microlitre)	260	262	260
N/L (%)	59/29	63.5/25.6	69/17
PCV (%)	37.8	40.4	40.2
MCV (fl)	88	90	90
MCH (pg)	29.8	30.7	30.4
MCHC (gm/dl)	33.8	34.0	33.8
CREAT (mg/dl)	1.16	1.06	0.80
UREA (mg/dl)	59.9	59	
BUN (mg/dl)	28	28	
BILI (T/D/I) [mg/dl]	0.5/0.3/0.2	0.5/0.3/0.2	0.5/0.3/0.2
SGOT (u/lit)	22	22	34
SGPT (u/lit)	19	19	30
ALK PHOS (u/lit)	44	44	51
PROT (T/A/G) [gm/dl]	7.1/2.9/4.2	7.1/2.9/4.2	5.9/2.5/3.4
Na^+ / K^+ / Cl^- (mmol/lit)	141/4.4/114	140/3.7/113	138/3.6/113
AMMONIA (micro gram/dl)	21		

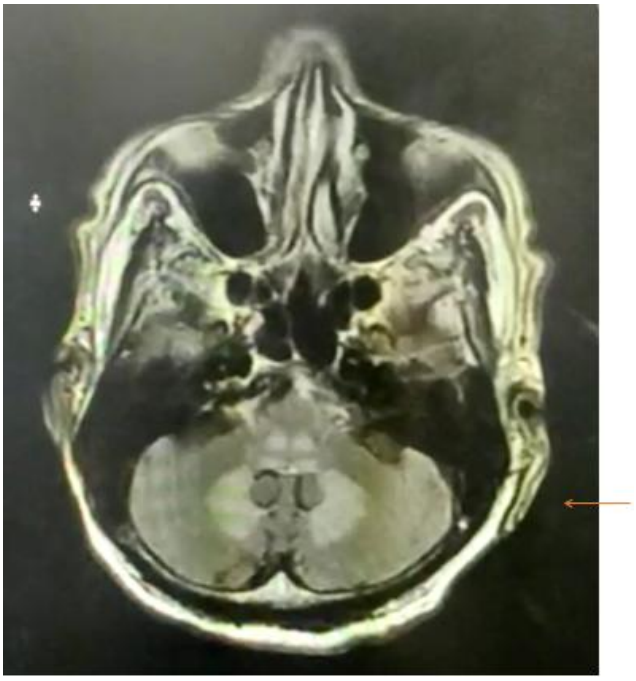

Figure 1: Bilateral Hyperintensities in the Dentate Nucleus

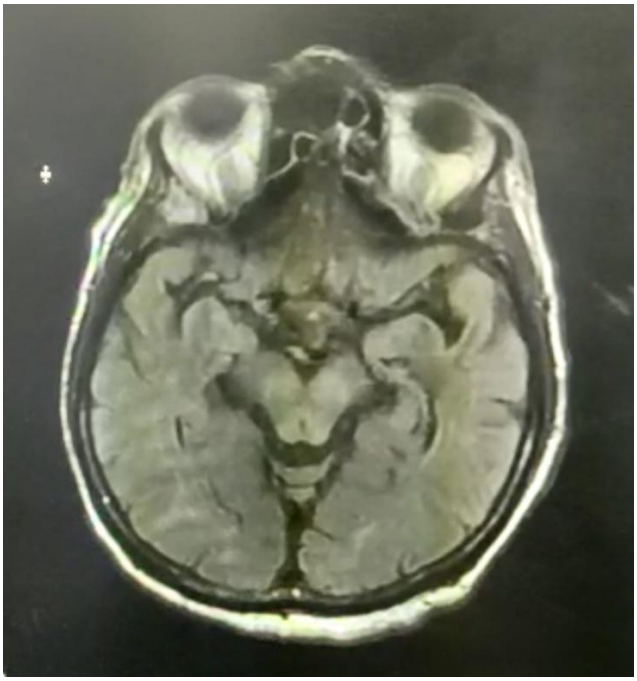

Figure 2: Bilateral Hyperintensities in Red Nucleus

Treatment

Tab Metronidazole was Stopped and within 48 hours of stopping the drug patient sensorium improved. After 24 hours of stopping the drug patient became oriented to person but not to time and place with GCS of E_4 V_4 M_6. After 48 hours he became oriented to Time, Place and Person with GCS of E_4 V_5 M_6 and Four Score of E_4 M_4 B_4 R_4. Patient was shifted to Tab Chloroquine 500 mg BD for 3 days followed by Tab Chloroquine 250 mg BD for 5 days. On serial USG Abdomen the size of the abscess reduced gradually.

3. Conclusion

Neurotoxicity is an important but rare adverse effect of Metronidazole. It is necessary to differentiate other conditions such as Demyelinating and metabolic diseases. Multiple sclerosis or acute disseminated encephalomyelopathy could produce diffuse encephalopathy but normal CSFand the selective involvement of cerebellar dentate nuclei make these diagnoses less likely. The possibility of Wernicke encephalopathy should also be considered as it tends to show a predilection for the midbrain and diencephalonand high signal intensities on DWI in the these areas. Our patient developed encephalopathy following the initiation of Metronidazole at High Dose and showed complete improvement after discontinuation. This temporal relationship supports the diagnosis ofMetronidazole Induced Encephalopathy.

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