ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 49. 23
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 3, Issue – 6, November - 2018, Page No. :128 - 131

Metronidazole Induced Reversible Neurotoxicity -A Rare Case.

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Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

Metronidazole is widely used for treatment of anaerobic bacteria and protozoal infection and relatively considered safe. Cerebellar neurotoxicity and peripheral neuropathy are rare adverse event in Patient treated with Metronidazole. We report clinical and radiological findings in 40 years old male who developed Metronidazole induced cerebellar neurotoxicity and peripheral neuropathy after prolonged cumulative dose of Metronidazole which was reversible after discontinuation of drug.

Keywords: Metronidazole, Drug induced cerebellar ataxia, Peripheral neuropathy.

Introduction

Metronidazole is a 5 -nitroimidazole with bactericidal activity against most anaerobic and facultative anaerobic bacteria and protozoa including Entamoeba, Giardia, Trichomonas, and B.coli ,H. Pylori and Guinea worm.it is relatively considered safe. The most frequently observed adverse effects of metronidazole are nausea, vomiting, metallic taste and epigastric distress. Neurological toxicity is rare and has included peripheral neuropathy, Headache, dizziness, syncope, vertigo, ataxia and confusion [1] Cerebellar toxicity reported and is very unusual manifestation of metronidazole toxicity. There are only few reports of metronidazole induced acute neurotoxicity and cerebellar dysfunction [2]. Duration of treatment before cerebellar symptoms manifest is variable, and cumulative doses range from 25 gm to 110 gm [3]. On the other hand Peripheral neuropathy is developed of 1 gm to 2.5 gm/day of Metronidazole, total of at least 50 gm over at least 30 days of duration [4-7].

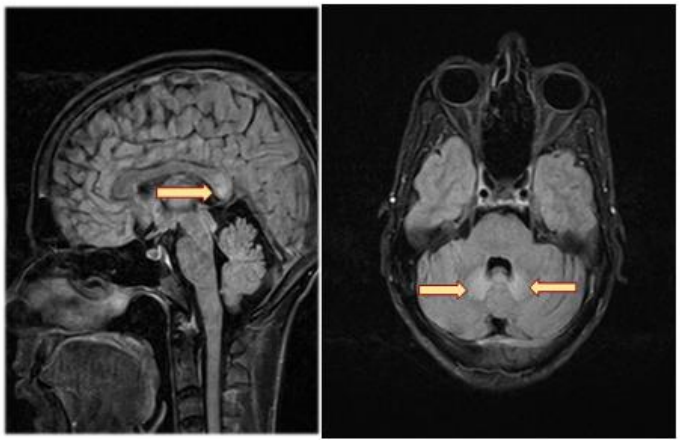
We report 40 Years old male who developed Metronidazole Induced Neurotoxicity with cerebellar signs and distal sensory neuropathy after prolonged cumulative dose of Metronidazole which was reversible after discontinuation of medication. Here we want to draw attention to rare adverse neurotoxicity induced by prolonged use of Metronidazole which physician should be aware to save patient from permanent disability.

Case Report

40 Years old male came with chief complaint of pain in abdomen since 15 days, which was acute in onset and was localized to right upper quadrant of abdomen and was radiating nature to right sided shoulder. Patient also complaint of fever which was mild grade and intermittent in nature for 15 days. he developed 3-4 episodes of vomiting per day, non-bilious, non-projectile since 10 days. Patient was admitted in surgery ward in view of abdominal pain. Ultrasound of abdomen was done was

suggestive of mild hepatomegaly with partially liquefied liver abscess of size 3.2x3.6x2.9 cm (VOLUME 18 CC) in segment II. Patient was started on 600 mg metronidazole thrice a day by intravenously. After 3 days patient developed unsteady gait and incoherent speech and burning sensation in bilateral lower and upper limbs. Patient was taken transferred to Medicine side for evaluation of Gait and speech abnormality. Patient was evaluated and investigated. On detailed history it was found that 1 month back patient had similar complaints of pain in abdomen and was found to have uniliquified liver abscess and was started on oral metronidazole 400 mg three times a day. patient continued taking metronidazole for one months without consultation for persistent pain in abdomen. There was no history of convulsions, trauma/fall, headache, neck pain. There was no history of Diabetes mellitus, Hypertension, Asthma or Tuberculosis in past. On clinical examination Patient was of average built and nutrition. There was no signs of anemia, Jaundice, cyanosis or clubbing. Vitals were stable with pulse -72 /min, Blood pressure – 122/70 MMHG Respiratory rate 16 cycles/min. There was no bony tenderness or swelling in spine.On Nervous system examination, Patient was conscious, cooperative well oriented. Speech was staccato.He had horizontal nystagmus of 4-5 beats on extreme lateral gaze. Left pupil was sluggishly reacting to light. Cerebellar testing revealed past pointing in finger nose test, Positive Romberg's sign and dysdiadochokinesia. No atrophy or hypertrophy of any muscle. Normal tone in all limbs. power was 5/5 in upper limbs and 4/5 in bilateral lower limbs. Sensory examination revealed loss of sensory modality in stocking and glove pattern. All tendon reflexes were present except bilateral ankle were absent. Gait was broad based, not able to stand with feet together, felt very unsteady and was unable to walk without support.

Serial routine blood investigations were normal including complete blood counts, liver function test and kidney function test and fasting blood sugar. CT scan of brain was normal. MRI brain and whole spine screening revealed bilateral symmetrical areas of alerted signal intensity in dentate nuclei, superior colliculus and splenium of corpus callosum on T2w and flair(Fig 1a and 1b).



In view of history of prolonged intake of Metronidazole and positive cerebellar signs diagnosis of Metronidazole induced neurotoxicity was established. Metronidazole was discontinued. Nerve conduction study showed presence of pure sensory axonal polyneuropathy affecting both lower limbs >upper limbs .After discontinuation of Metronidazole patient's speech become coherent and was able to walk with support within 3 days .Review ultrasound of abdomen was suggestive of resolving liver abscess and patient was discharged .On 3 weeks of follow up patient is doing better and able to walk without support but sensory neuropathy till persist .

Discussion

Metronidazole is 5 -nitroimidazole with activity against anaerobic and facultative anaerobic and protozoa. Metronidazole is widely used drug for treatment of anaerobic and protozoal infection. Liver abscess are caused by bacterial, parasitic of fungal infection [8] Out of this amoebic and pyogenic abscess are most common. In

India, due to poor sanitary condition and a lower socioeconomic status, amoebiasis is endemic and amoebic liver abscess accounts for 3-9% of all cases of amoebiasis[9].For both pyogenic and amoebic liver abscess Metronidazole is mainstay of treatment[8]. The most frequently observed adverse effects of metronidazole are nausea, vomiting, metallic taste and epigastric distress. Neurological toxicity is rare and has included peripheral neuropathy, Headache, dizziness, syncope, vertigo, ataxia and confusion [1], cerebellar signs and symptoms and encephalopathy[10]. Cerebellar toxicity is very unusual manifestation of Metronidazole[11] therapy and cumulative doses of 25 gm to 110 gm of Metronidazole for cerebellar toxicity [3] and Peripheral neuropathy is developed of 1 gm to 2.5 gm/day of Metronidazole, total of at least 50 gm over at least 30 days of duration[4-7].AS in our case there was cerebellar neurotoxicity with peripheral neuropathy after consuming approximately 48 gm of Metronidazole over almost one and half months .

Ahmed et al was first to describe metronidazole induced neurotoxicity in 1995, as fairly symmetric abnormal signals within supratentorial white matter , including the corpus callosum , and within the cerebellum , including cerebellar deep grey matter nuclei[2] .It has been proposed that axonal swelling with increased water content causes the MRI changes due to T2 prolongation , hence accounting for rapid reversibility of changes upon cessation of drug[2] .The typical locations of lesions in metronidazole induced encephalopathy are the cerebellar dentate nuclei ,tectum ,red nucleus ,tegmentum ,dorsal pons and medulla and splenium of corpus callosum and lesions are mostly bilaterally symmetrical[12].This increased signal intensity is observed on T2W/FLAIR sequences[10] as in our patient ,T2w/FLAIR sequence was suggestive of bilateral symmetrical areas of alerted signal intensity in dentate nuclei, superior colliculus and splenium of corpus callosum.The mechanism of metronidazole induced toxicity is controversial .It is postulated that metronidazole and its metabolites were found to bind selectively with neuronal ribonucleic acid(RNA),and inhibit protein synthesis causing axonal degeneration[4].Other suggested mechanism include following ,modulation of gamma amino butyric acid(GABA)by intermediate metabolite of metronidazole in central nervous system , or free radical injury to nerve tissue[13] .In a prospective study for evaluation of metronidazole induced toxicity it is found that the cumulative dose of metronidazole was low(15-20 gm) and latency of symptoms onset is very short (12-18 days) as compared to patients from west[14].This reflects a genetic susceptibility to neurotoxic effects of metronidazole or genetic variation in metronidazole metabolism in Indian patient .

The differential diagnosis of bilateral symmetric T2 hyper intense lesion in dentate nuclei is Methyl bromide intoxication, Maple syrup urine disease and enteroviral encephalopathy[10]. The diagnosis of metronidazole encephalopathy is established by MRI findings in conjugation with clinical findings and significant treatment history. Symptoms of encephalopathy improve within days of stopping metronidazole while neuropathy may persist for months[12]. as in our case, patient's cerebellar neurotoxicity was resolves within 3 days but peripheral neuropathy still persist on 3 months of follow up.

Metronidazole should be used with some caution and with clear indication especially during prolonged course and when prescribed in relatively large dose ,clinician must be aware of possible neurotoxic side effects to prevent permanent disability.

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