ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 11 | November - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

METRONIDAZOLE INDUCED NEUROTOXICITY: A CASE REPORT

Neurology

Tarun Sharma Senior Resident, SNMC Jodhpur
Roopakshi Pathania Senior Resident, SNMC Jodhpur
Deep Patel Senior Resident, SNMC Jodhpur
Shubhakaran Khichar Professor, SNMC Jodhpur

ABSTRACT

We report a case of metronidazole induced CNS as well as peripheral nervous system toxicity with clinical and radiological findings which resolved following stoppage of metronidazole. She had history of metronidazole intake for liver abscess.A high index of clinical suspicion,temporal relationship and characterstic MRI and supportive NCV findings helped to make the diagnosis.

KEYWORDS

INTRODUCTION

Metronidazole is commonly used nitroimidazole antimicrobial agent for wide variety of anaerobic and parasitic infections.Commonly it doesnot cause any serious side effects.However in some patients toxicity can be seen with higher predilection in those with longer duration of treatment(average period 6-7weeks) like liver abcess or higher cumulative dose(5-2000g).It easily penetrates the blood brain barrier and accumulates leading to toxicity. Toxicity has a wide spectrum from CNS and peripheral nervous system manifestations and are reversible.

Case Summary

A 53 year old female patient rt.handed housewife, without any comorbidity presented with c/o Gradual onset symmetrical sensory motor parapareisis distal>proximal since one year.On examination she had decreased bulk in distal upper limb&lower limb,POWER-5/5 in upper limb Lower limbs 4/5 hip joint and 3/5 knee joint ANKLE-dorsiflex 3/5and planterflex 2/5 .B/L ankle jerks were absent, planter-mute b/l.Decreased pain and temperature by 20% below knees.She had history of liver abscess 1year ago patient took tab metronidazole (1600mg daily for 30days) along with pigtail catheter insitu for 7days. After1 month of metronidazole (c.d.around48gm) Patient was admitted for recurring vomiting followed by altered sensorium which recovered in 2-3 days . MRIbrain 14/9/2021 Symmetric restricted diffusion in subthalamus,midbrain,dentate nucleus and anterior and posterior part of corpus callosum ??toxic metabolicen-cephalopathy>>>Wilsondisease. Wilsons disease workup was negative. Patient was managed as wernickes encephalopathy. Metronidazole dose tapered off 800mg for 4months.Patient is off metronidazole since four months.Her baseline including TSH/ B12/CPKNAC normal.NCV S/O sensorimotor axonal polyneuropathy.EMG NORMAL STUDY..MRI BRAIN:22/07/22 Residual bilateral symmetric faint signal alteration of medulla oblongata and genu of corpus callosum.Radiologic improvement of previously noted acute metabolic toxic encephalopathy.MRI CERVICAL SPINE normal.

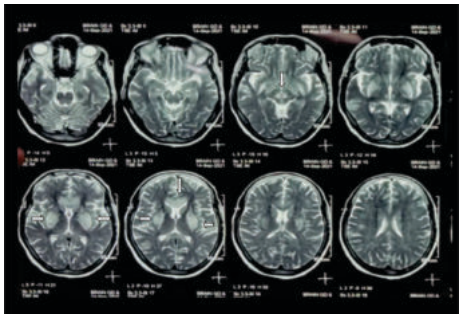

Figure 1 AXIAL T2W MRI Shows Symmetric Hyperintensities In Bilateral Subthal Amus, Midbrain, And Pons

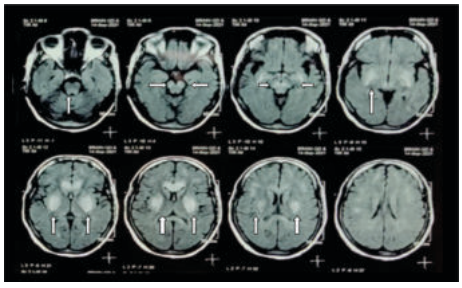

Figure 2 Axial Flair Mri Shows Symmetric Hyperintensities In Bilateral Subthal Amus, Basal Ganglia,corpus Callosum, Midbrain, And Pons

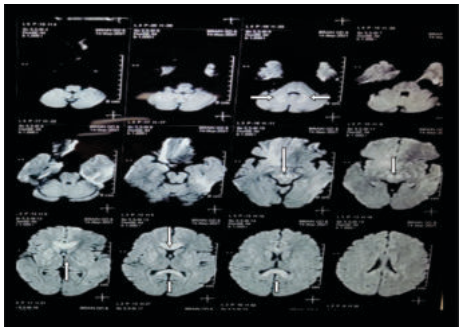

Figure 3 Axial Dwi Images Showing Diffusion Restriction Corpus Callosum And Midbrain.

DISCUSSION

Metonidazole is widely used antiparasitic and antibacterial agent,mostly for anaerobic infections.It is a nitroimidazole antibiotic and has been available for clinical use for more than 30 years. In case–control study, the incidence of neurologic events was 0.25%, although this is likely an underestimate.[1]

Common adverse reactions,include nausea, dry mouth, vomiting, and diarrhea. Neurotoxicity is rare features include ataxia, dysarthria and altered mental status, but rarer manifestations such as seizures, encephalopathy and cerebellar dysfunction have also been described.[2] Patients with central nervous system abnormalities have coexisting peripheral neuropathy in roughly one-third of cases manifesting as diminished sensation, numbness and neuropathic pain. Average duration of treatment before symptom onset is 6–7 weeks,but can appear within days of initiation.[2,3]

Patients receiving metronidazole for inflammatory bowel disease,

osteomyelitis and large, undrained abscesses are at greatest risk of neurotoxicity due to long exposure. A review of 110 adult cases with metronidazole induced encephalopathy found the median cumulative dose was 65.4 g, although there was wide variability (range 5–2000 g).[3] The duration of treatment with metronidazole before cerebellar symptoms manifest is variable, and cumulative doses range from 25 g to 110 g .[4]

MR imaging in patients with MIE are the cerebellar dentate nuclei, midbrain (tectum, red nucleus, and tegmentum around periaqueductal gray matter), dorsal pons (the vestibular nucleus, a focal tegmental lesion of the superior olivary nucleus, and the abducens nucleus), dorsal medulla, and corpus callosum (splenium); and these lesions were always bilateral and symmetric. Uncommon locations were the inferior olivary nucleus and the white matter of the cerebral hemispheres.[5]

Axonal swelling has been suggested as one possible mechanism for CNS findings likely a result of localized vasogenic edema, as opposed to ischemia or demyelination[6].High doses in rats induce lesions in cerebellum; these alterations were topographically comparable to central nervous system lesions induced by thiamine deficiency in rats and in Wernicke's encephalopathy in humans. Studies in dogs have found Purkinje cell lesions after prolonged metronidazole administration and other studies in mice have revealed carbon-labeled metronidazole detected in the cerebellum[6,7.]

Toxic neuropathies generally result in length dependent axonal neuropathy with the exception of diphtheria and a few toxic neuropathies. They are often misdiagnosed as no easily available specific or biological tests for diagnosis.They are suspected on basis of clinical examination and electrodiagnostic features. The Bradford Hill criteria define a systematic approach for assessing the issue of causation. Before an agent is implicated to cause neuropathy, there must be strong association between the toxin and neuropathy, temporal relationship, dose response relationship, improvement following removal from exposure, animal model, a consistent clinical spectrum across studies, and biological possibility. More the criteria are met; stronger is the association between the toxin and neuropathy. The diagnosis of toxic neuropathy may be complicated by progression of neuropathy for weeks or months even after cessation of exposure which is known as coasting effect.[8] In animal experiments, Bradley et al. found that metronidazole and its metabolic product could bind to RNA and inhibit protein synthesis, resulting in axonal denervation in nerve fibers[9].Metronidazole should be used with caution and clear indications, particularly during prolonged courses and when prescribed in large doses. We suggest that a careful neurological examination and EMG study should be performed in patients who complain of symptoms of peripheral neuropathy during treatment with metronidazole[10]

Management consists of withholding metronidazole and changing to alternative therapy fepending on culture and sensitivity.

However where a 5-nitroimidazole is indispensable, replacement with other 5-nitroimidazole like tinidazole or ornidazole may be tried, 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.[11] In few cases methylprednisolone has been tried where patient detiorated following stoppage of metronidazole,however further research is needed to confirm role of steroids in metronidazole toxicity.

CONCLUSION

Metronidazole should be used with caution and clear indications, particularly during prolonged courses and when prescribed in large doses. We suggest that a careful neurological examination and EMG study should be performed in patients who complain of symptoms of peripheral neuropathy during treatment with metronidazole. 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.

Declaration Of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed

Financial or Other Competing Interests

None.

REFERENCES

1. Metronidazole-induced neurotoxicity Danica Quickfall MD CM, Nick Daneman MD, Adam A. Dmytriw MD MPH, David N. Juurlink MD PhD Cite as: CMAJ 2021 October 25;193:E1630. doi: 10.1503/cmaj.201671
2. Metronidazole associated neurologic events: a nested case-control study. Daneman N, Cheng Y, Gomes T, et al Clin Infect Dis 2021;72:2095-100.
3. Metronidazole induced encephalopathy: a systematic review Sørensen CG, Karlsson WK, Amin FM, et al. J Neurol 2020; 267:1-13.
4. Chakrabarti S, Pan K. Metronidazole-induced encephalopathy: an uncommon scenario. NZMJ. 2014;127(1393) ISSN 1175 8716 [PubMed] [Google Scholar] [Ref list]
5. MR Imaging of Metronidazole-Induced Encephalopathy: Lesion Distribution and Diffusion-Weighted Imaging Findings ,E. Kim, D.G. Na, E.Y. Kim, J.H. Kim, K.R. Son and K.H. Chang;American Journal of Neuroradiology October 2007, 28 (9) 1652-1658; DOI: https://doi.org/10.3174/ajnr.A0655
6. Cerebellar ataxia following prolonged use of metronidazole: case report and literature review KalpeshkumarPatelaIsraelGreen-HopkinsaStanleyLubAllan R.Tunkela; International Journal of Infectious Diseases,Volume 12, Issue 6, November 2008, Pages e111-e114
7. K. Scharer ;Selective injury to Purkinje cells in the dog after oral administration of high doses of nitroimidazole derivatives;Verh Dtsch Ges Pathol, 36 (1976), pp. 930-936
8. Toxic neuropathies:Indian perspective Year : 2009 | Volume : 57 | Issue : 6 | Page : 697-705 Usha Kant Misra, Jayantee Kalita Department of Neurology, Sanjay Gandhi PGIMS, Lucknow, India
9. Bradley W, Karlsson I, Rassol C. Metronidazole neuropathy. Br Med J 1977;2:610-1.
10. Goolsby TA, Jakeman B, Gaynes RP. Clinical relevance of metronidazole and peripheral neuropathy: A systematic review of the literature. Int J Antimicrob Agents 2018;51:319-25
11. Clinical and Neuroradiological Spectrum of Metronidazole Induced Encephalopathy: Our Experience and the Review of Literature; Ujjawal Roy1, Ajay Panwar2 et al, DOI: 10.7860/JCDR/2016/19032.8054
12. A case of methylprednisolone treatment for metronidazole-induced encephalopathy ;Li Li1,2, Xiaogang Tang1, Wenlei Li1, Seng Liang1, Qing Zhu1 and Minghua Wu1,2*Li et al. BMC Neurology (2019) 19:49 ;https://doi.org/10.1186/s12883-019-1278-6