CASE REPORT

JIACM 2022; 23 (3-4): 136-139

Metronidazole-induced Reversible Cerebellar Syndrome in Two Brothers (Neo Postulation for Drug-Cerebellar Toxicity)

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Abstract

Reversible cerebellar syndrome caused by metronidazole observed in two brothers of a family who received the drug for enteritis. The metronidazole toxicity seems not related to cumulative dose or duration related phenomenon. Postulations suggested in literature for the development of cerebellar toxicity are discussed. A newer hypothesis is discussed and described based on analysis carried out on molecular docking, drug metronidazole 3D structure, and its binding affinity with structural gene, potassium voltage gated channel interacting protein (KCNIP4). Visualization is done with the ball and stick model of metronidazole with KCNIP4 gene using CHIMERA software.

Key words: Metronidazole, cerebellar toxicity, molecular docking, KCNIP4 gene, 3D structure.

Introduction

Metronidazole, a bactericidal and anti-protozoal antibiotic is widely used in clinical practice for trichomonal, amoebic infections, hepatic encephalopathy, *H. pylori* infections, *Clostridium difficile*, etc. Though the drug is safe, but peripheral/CNS toxicity has been reported uncommonly irrespective of the dose and duration of its consumption. Most of the adverse effects are reported early in the course, and disappear within weeks of discontinuation of the therapy. Flair MRI T2W scan findings revealing hyperintensities within dentate nuclei of cerebellum are characteristically described with reversible cerebellar syndrome[1]. The proclivity to understand the mechanisms of action of metronidazole-induced neurotoxicity, its adverse effects with cerebellar involvement, described earlier by many workers remains poorly understood[2,3]. Dose and duration of the drug in development of toxicity is also debatable. A newer formulated mechanism is proposed as regards the development of cerebellar toxicity and symptoms reversibility on drug withdrawal. The study encased utilising binding affinity of the drug and features of structural gene KCNIP4 docking with the drug[4,5]. For the purpose CHIMERA software was used.

Case 1

A 24-year-old male patient before presenting to this hospital was hospitalised in a private nursing home for enteritis; he was given tablet metronidazole 400 mg three times daily for 3 days. He was transferred to the present hospital with features of slurred speech, head nodding, ataxic gate, dysmetria. The cerebellar involvement was more on the right side than left. On examination, he was found to have head nodding, dysarthric speech, unsteady gate, dysmetria and slow horizontal nystagmus. Patient had bilateral involvement with predominant involvement of the right side. Patient was alert and oriented to senses. Vibration sensations were intact. Rhomberg's sign was negative. Blood counts and haemogram were within normal limits. NMO antibodies (IgG and IgM) were negative. MRI findings on bilateral symmetric T2 FLAIR showed hyperintensities in the dentate nuclei of cerebellum and central medulla, features considered typical of drug toxicity (Fig. 2).

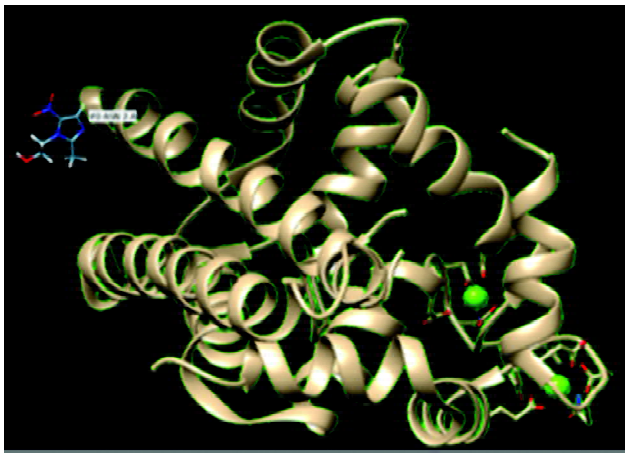

Fig. 1: *The figure shows ball and stick model of drug metronidazole with KCNIP4 gene, visualised with 3D structure and CHIMERA Software. The drug is having bond with leucine and aspartic acid on position 1 and 2 of KCNIP4 gene.*

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Realizing the patient is having metronidazole cerebellar syndrome, the drug was discontinued. Soon after 3 days of discontinuation of therapy, the patient gained his stance. The symptoms had gradually improved. Patient was completely alright after 15 days. Second MRI was not considered as patient had a near complete improvement.

The cumulative dose of metronidazole consumed in 3 days was approximately 4.5 grams.

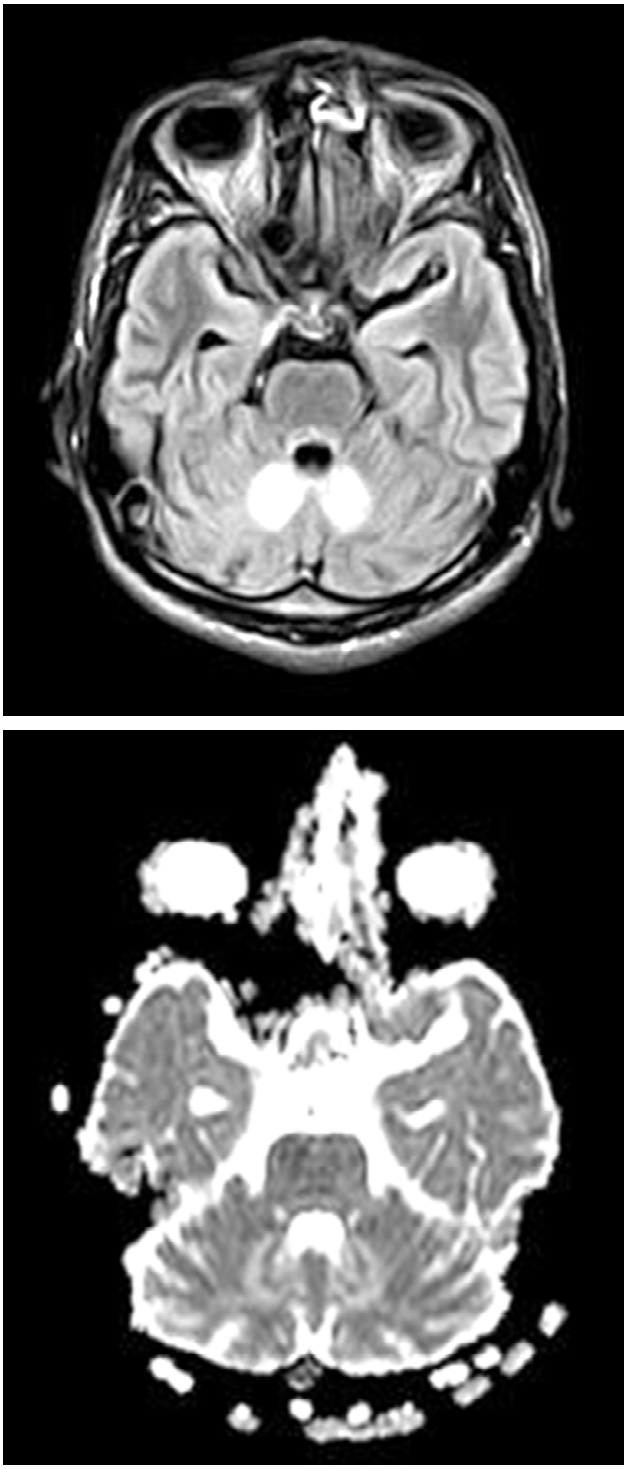

Fig. 2: *FLAIR and T2WI of MRI brain showing Hyperintense Signal intensity is noted in bilateral dentate nuclei and posterior part of pons.*

Case 2

A 22-year-male patient, brother of Case 1 who presented

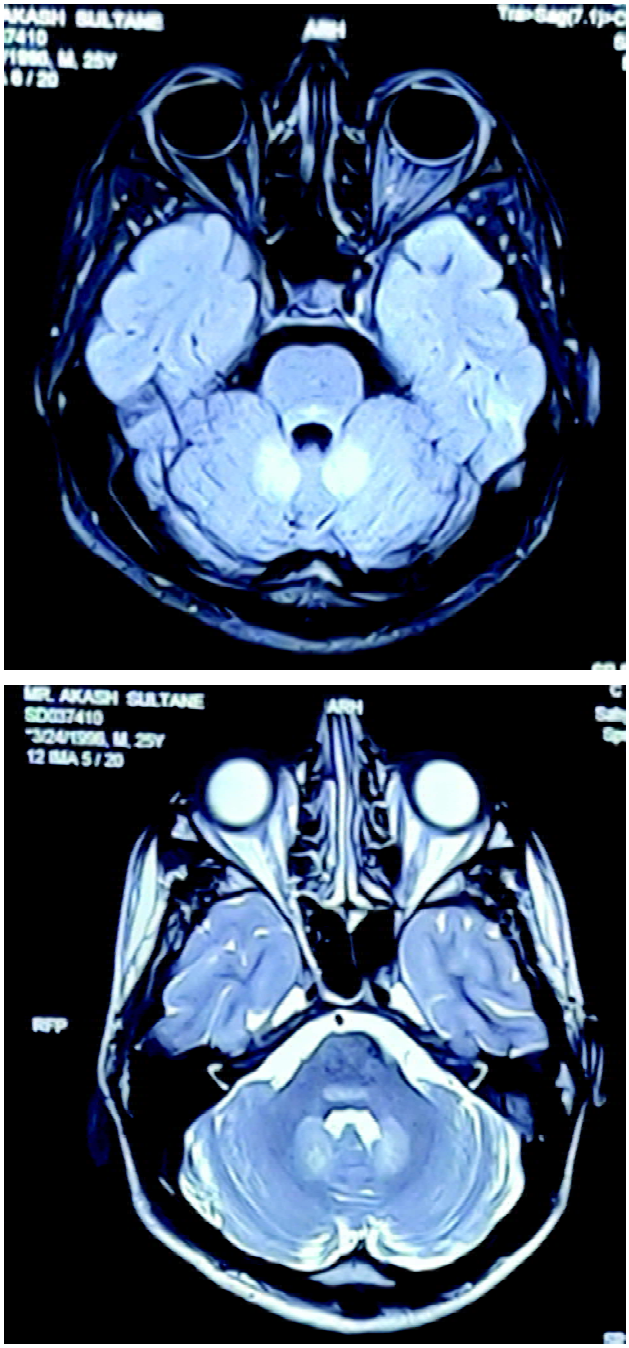

Fig. 3: *FLAIR and T2WI of MRI brain showing Hyperintense Signal intensity is noted in bilateral dentate nuclei and posterior part of pons.*

with features of cerebellar syndrome. The history revealed consumption of tablet metronidazole 500 mg three times daily for 4 days. He was transferred to this hospital for ataxia, slurred speech, and tremors of both hands. On neurologic examination, he was alert, well oriented, deep reflexes were intact, sensations including posterior column were within normal limits. Plantar reflexes were flexor, Rhomberg's sign was negative. Speech was dysarthric, minimal horizontal nystagmus on lateral gaze was noted; there was no vertical nystagmus. Pupils were reactive to light.

Cerebellar testing revealed finger-to-nose testing, dysdiadochokinesia, heal to shin manoeuver were bilaterally affected. Pendular jerk was more evident on the left side.

MRI brain revealed symmetrical altered signals, noted in bilateral dentate nuclei of cerebellum, central medulla and pons appearing hyper on T2W image and FLAIR showing restriction in cerebellar lesion(Fig. 3). Features were suggestive of drug neuro toxicity. The drug was discontinued; clinical improvement was noted after 5 days of discontinuation; and complete recovery after 20 days. Patient refused for a follow-up MRI.

The cumulative dose of metronidazole was approximately 6 grams which he consumed in 4 days.

Discussion

Metronidazole is a 5-Nitroamidazole drug having potent bactericidal activity against widely covered anaerobic bacterial and protozoal infections. The drug is often well tolerated. Most frequently occurring adverse effects are gastrointestinal. Central neurotoxicity is uncommon but events are serious as they develop encephalopathy, seizures, altered mental status and cerebellar syndrome. The possible mechanisms of metronidazole drug hypothesis include:-

1. Binding of metronidazole to neural RNA that inhibits protein synthesis.
2. Modulation of inhibitory neurotransmitter gamma aminobutyric acid receptor within vestibular and cerebellar mitochondrial dysfunction.
3. Others have postulated axonal swelling, vasogenic and cytotoxicity leading to localised oedema detected on MRI[2]. The findings are opposed to ischaemia and demyelination.
4. As the drug is structurally similar to thiazole, a precursor of thiamine, it could lead to reduction in thiamine absorption by acting as a thiamine analogue[6].

We presently encountered two cases in male brothers aged 24 and 22 years, who developed features of cerebellar syndrome with dysarthria, dysmetria, ataxic gaite and nystagmus three days after receiving metronidazole drug with a cumulative dose of 3.6 grams to each for enteritis under hospitalisation. The symptoms regressed soon and we noticed total recovery within 15 days of discontinuation fo the drug in Case no. 1, the elder brother; and it took 20 days for the younger brother for achieving total recovery. The available literature describes the cumulative dose with varying range from 25 to 1,080 grams of the drug and resolution of symptoms in 1 - 3 months after cessation of the medication[3].

In this study, the drug metronidazole's 3D structure was used, for assessing the binding affinity of the drug with structural gene KCNIP4. This gene is a potassium voltage gated channel interacting protein-4 that encodes a member of a family of voltage gated potassium channel interacting proteins. The binding affinity of the gene KCNIP4 is blocked by the drug at the end/edge of aspartic acid and leucine at position 1 and 2 at the heads not permitting any other molecule or the compound to bind this region. This inhibitory reaction and binding mechanism results to effect the energy production for cell maintenance and normal regulation. The binding position which are at 1 and 2 of leucine and aspartic acid bind through hydrogen ion bonds which are considered weak bonds in cell regulatory mechanism. When the drug consumption is stopped, the binding bonds of the drug with the gene end and remain distracted as the bonds are weaker. The gene then functions in a normal way. The neurologic symptoms hence abate. We feel deeply ingrained in offering a possible new tentative explanation/ mechanism for development of reversible drug-cerebellar toxicity.

Whether the studied gene bears any familial functional significance could not be assessed. The Case 1, 24 years and Case 2, 22 years are brothers of the same family, deny history of familial, genetic, or any allergic disorders. Both the brothers suffered with cerebellar ataxia post-metronidazole therapy for enteritis. They recovered from the symptoms soon after omission of the drug. Our above-mentioned hypothesis is found to be novel as has not been described by any other researcher.We tried to highlight the binding position where the drug under discussion alter/ induce the reactionary mechanism by blocking the binding sites (position 1 and 2 of aspartic acid and leucine). Otherwise, the same sites could bind the different molecules to produce energy for cell functioning. KCNIP4 gene was extracted from Gene card database after screening 50 plus genes involved in Genetic testing in ataxia[4].

The newer proposed outcome of drug with KCNIP4, a potassium voltage gated channel interacting gene, needs

further analysis on CHIMERA Software details with cases of similar type.

Conclusion

Metronidazole-induced cerebellar dysfunction is an uncommon occurrence though the drug is safe. However, the adverse reactions are reported early in the course and disappear within weeks of discontinuation of the therapy. The mechanism described earlier by many workers remains poorly understood. The present study describes yet another tentative explanation/mechanism based on data based screening, analysis carried-out on molecular docking, the drug's 3D structure and its binding affinity with potassium-gated voltage channel interacting protein KCNIP4 gene.

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