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Indian Journal of Medical Sciences

Original Article

Metronidazole-related neurotoxicity in a referral hospital

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ABSTRACT

Objectives: Metronidazole is commonly used drug in almost all the fields of medicine. Commonly patients use medication for a shorter time than was prescribed, but in this report, the patients have used medication for long time based on ultrasound images. This study aims to assess metronidazole-related neurotoxicity at this hospital.

Material and Methods: All the patients with diagnosis of amebic liver abscess, who developed neurotoxicity with metronidazole, were evaluated retrospectively.

Results: Ten patients with metronidazole neurotoxicity were seen from April 2017 to March 2019. All ten had peripheral neuropathy; one each had in addition cerebellar ataxia and new onset seizures.

Conclusion: A preventable toxic effect with metronidazole has to be recognized early during drug therapy for hepatic amebic abscesses. A dose adjustment during therapy helps in preventing this neurotoxicity. The patients have to be educated that metronidazole should not be continued on ultrasound images.

Keywords: Amebic liver abscess, Metronidazole, Neurotoxicity, Neuropathy, Cerebellar ataxia

INTRODUCTION

Not many case series have been reported with metronidazole neurotoxicity from India. There are a large number of amoebic liver abscess cases in community treated in the tropics, but there are occasional case reports or few cases series.[1,2] In a web-based search (MEDLINE/PubMed, EBSCO, and Google Scholar) through February 2017 using the search terms metronidazole and peripheral neuropathy, or polyneuropthy, or paresthesia, or neurotoxicity by Goolsby *et al.*, only 93 references were available.[3] In this systematic review article, metronidazole-associated neurotoxicity incidence was unknown, and a varying rate of 0–50% was reported in different series.[3] There was a good correlation between the dose and duration of metronidazole therapy and neurotoxicity. A higher dose of more than 42G treatment course and more than 4 weeks duration was associated with neuropathy.[3] Other neurotoxicities such as cerebellar ataxia, seizures, and encephalopathy are rarely reported.[2,4,5] We report a series of ten cases seen in last 2 years from ILBS.

MATERIAL AND METHODS

Institute of Liver and Biliary Sciences is a referral institute for liver diseases in India. The patients from all over the country are referred here if they require highest category liver care and work up. The data were collected from outpatient follow-up clinic and neurophysiology laboratory of the institute. These patients presented with symptoms of neuropathy in form of numbness, tingling, pain, and difficulty walking while on treatment for amebic liver abscesses. All the patients were treated outside first and when they did not recover, they were referred for final evaluation and treatment at ILBS. An accurate dose of metronidazole was not clear. A proper metronidazole treatment was advised (800 mg 3 times a day for 7 to 14 days) depending on the severity of the illness. We arrived at the cumulative dose when the patients informed us total number of tablets taken in the whole illness. The patients had started with symptoms of tingling, numbness in feet, and hands after a month on metronidazole treatment. In view of the seriousness of the underlying disease, the patients continued metronidazole. When the total dose of medication for the illness was calculated; invariably, it was above 42 g in each patient. The patients were advised nerve conduction velocity and evaluated after completion of the therapy with metronidazole. After proper neurological examination, upper and lower limb motor and sensory nerves were tested. For this study distal latency, compound muscle action potential

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Received: 08 September 2020 **Accepted:** 20 November 2020 **EPub Ahead of Print:** 22 December 2020 **Published:** 24 September 2021 **DOI** 10.25259/IJMS_267_2020

(CMAP) and velocity of the right tibial nerves in each patient were taken for the motor conduction study, while right sural nerve measurements of distal latency, sensory action potential (SAP) amplitude, and velocity were taken for sensory conductions. The values were compared with the normal data available in the neurophysiology laboratory.

RESULTS

In the ten patients seen at this institute, age ranged between 28 and 69 years, mean age of 50.2 years. Eight out of ten cases were males (80%). A total of 10 cases and 8 controls were studied. The average age of the cases was 52.1 ± 5.2 years and among controls was 53.6 ± 2.9 years. Nearly 20.0% of the cases and 50.0% of the controls are women Table 1.

There were two patients with diabetes mellitus on treatment and had good control of their diabetes. The patients had started with symptoms of tingling, numbness in feet, and hands after a month on metronidazole treatment. Examination revealed mild weakness of lower limb distal muscles and weak grips in eight of ten patients. Other two had symptoms of numbness and tingling but no weakness. Distal areflexia was seen in all patients. Nerve conduction study revealed axonal neuropathy in all motor and sensory nerves of upper and lower limbs. The lower limbs were affected more than the upper limb nerves. The nerve conduction velocities and CMAP and SAPs were significantly decreased when compared to the normal control for the ages [Tables 2 and 3]. The controls were taken from our own hospital that had undergone nerve conduction study. In control group, age range was 41–67 years with a mean age of 53.7 years. Statistical analysis revealed significant delay in distal latencies and compound action potential of tibial and sural nerves, respectively [Table 4]. One patient had associated cerebellar ataxia and another patient had new onset seizures. MRI brain images in both these patients were unremarkable. Vitamin B 12 levels were normal in all. Out of ten patients, only seven visited on follow-up. Four had had recovered in 3 months time. Other three had improved with some residual sensory disturbances. Cerebellar ataxia patient had completely recovered on follow-up.

DISCUSSION

Metronidazole is a synthetic 5 nitroimidazole antibiotic. It is used in anaerobic and protozoal infections. Metronidazole is the drug of first choice in amebic liver abscess and the usual treatment is 500–750 mg intravenous or oral 8 hourly for 7–14 days.[6] Most of the initial and minor side effects such as dizziness, metallic taste in mouth, nausea, and vomiting are usually ignored by the patients. However, longer use and larger doses result in serious neurological side effects.[3,7,8] In our series, the patients had invariably long treatment course lasting from 6 weeks to 8 weeks. This was due to improper dosages given outside. In addition, the patients were continued outside on metronidazole based on ultrasound abdomen findings. It is well known that after evacuation or treatment of the amebic abscess, the liver ultrasound changes take three to 6 months to disappear. Earliest reference to metronidazole neuropathy was in 1976.[9] Goolsby *et al*. made a web-based search (MEDLINE/PubMed, EBSCO, and Google Scholar) through February 2017 using the search terms metronidazole and peripheral neuropathy, or polyneuropthy, or paresthesia, or neurotoxicity.[3] In this search relevant case reports, retrospective studies, surveys, and review articles were included in the study. Bibliographies of all relevant articles were reviewed for additional sources. Only 93 references were available.[3] The review found 36 case reports (40 unique patients) of metronidazole-associated peripheral neuropathy, with most cases (31/40) receiving a >42 g total (>4 weeks) of therapy. In addition in this review in 13 clinical studies varying rates of peripheral neuropathy from 0 to 50% were seen.[3] A correlation of peripheral neuropathy was found in patients receiving >42 g total (>4 weeks) of metronidazole compared with those patients receiving ≤42 g total (17.9% vs. 1.7%). It was found that nearly all patients had complete resolution of symptoms on follow-up. Overall incidence of peripheral neuropathy associated with metronidazole is unknown.

Table 1: Gender distribution of the study population.

Characteristics of the subjects	Cases mean±SD or *n* (%)	Controls *n* (%)	Total *n* (%)
Gender			
Male	8 (80)	4 (50)	12 (66.7)
Female	2 (20)	4 (50)	6 (33.3)
Total	10 (100)	8 (100)	18 (100)

Table 2: Nerve conduction velocity features in patients.

No.	Age/ sex	Tibial nerve dl in ms	CMAP mvs	NCV m/s	Sural nerve dl in ms	SAP uvs	NCV m/s
1	64/F	6.15	3.9	37.5	3.25	2.5	43.1
2	55/F	5.95	4	40.5	3.3	3.3	42.5
3	48/M	6.1	3.6	36.6	2.9	8.8	48.3
4	53/M	4.35	4.8	34.6	3.75	2.3	37.3
5	69/M	5.05	7.9	41.1	No response	No response	
6	57/M	5.15	7.5	41	No response	No response	
7	55/M	4.3	3.4	39.1	No response	No response	
8	23/M	3.55	7.5	45.4	3.35	2.5	41.8
9	50/M	4.55	4.3	44.3	No response	No response	
10	28/M	Not done					

Table 3: Controls.

No.	Age/ sex	Tibial nerve dl in ms	CMAP mvs	NCV m/s	Sural nerve dl in ms	SAP uvs	NCV m/s
1	63/F	4.35	5.8	50.7	2.4	9.3	58.3
2	55/F	4.85	10.2	45.7	3	5	46.7
3	50/F	4.75	11.4	49.3	3	6.8	46.7
4	41/F	4.85	10.6	45.5	3.2	5.5	43.8
5	58/M	4.8	6.8	51.2	3.2	5.4	43.8
6	55/M	4.55	4.8	48.3	2.85	18	49.1
7	53/M	4.8	8.4	50.6	2.65	17.1	52.8
8	41/M	3.7	6.6	45.2	3.05	5.4	45.9

dl: Distal latency, ms: Milliseconds, CMAP: Compound muscle action potential, mvs: Mill volts, NCV: Nerve conduction velocity/s-meters per second, SAP: Sensory action potential, uvs: Micro volts

Table 4: Nerve conduction study among the study participants.

Nerve conduction study parameter	Cases median (interquartile range)	Controls median (interquartile range)	*P*-value
Tibial nerve			
Distal motor latency (ms)	5.05 (4.3–6.02)	4.75 (4.025–4.82)	0.23
Compound muscle action potential amplitude (mv)	4.3 (3.7–7.5)	8.4 (6.2–10.4)	0.011*
Motor conduction velocity (m/s)	40.5 (37.05–42.7)	48.3 (45.6–50.6)	<0.001*
Sural nerve			
Distal latency (ms)	2.9 (0–3.3)	3 (2.75–3.1)	0.931
Sensory action potential (uvs)	2.3 (0–2.9)	6.8 (5.4–13.2)	0.001*
Nerve conduction velocity (m/s)	37.3 (0–42.8)	46.7 (44.8–50.9)	0.001*

*Significant when tested by Mann–Whitney U-test

One patient in our series had features of cerebellar ataxia. His MRI brain was normal. Cerebellar ataxia is a rare feature of neurotoxicity and has been reported before.[4,8,10] The ataxia had completely improved on follow-up. One patient had generalized tonic-clonic seizures for the first time when on metronidazole. His EEG and MRI brain were normal. This association is rare and the mechanism is not known.[2] Encephalopathy features and seizures have been reported in the past on metronidazole.[2,5,10] In a detailed clinical, neuroimaging, and pathological features reported on two cases with encephaloneuropathy, diffuse changes in basal ganglia, dentate nuclei and white matter in the brain and vasculitic changes and axonopathy in peripheral nerves have been seen.[11] The exact mechanism of neurotoxicity is unclear.[11] Several theories have been postulated. Direct neurotoxicity on brain and peripheral nerves, RNA, and DNA binding of metronidazole or its intermediate metabolites affecting neural protein synthesis and mitochondrial function have been considered.[11] However, all the MRI brain changes seen in the previous reported patients were reversible. In the two cases in this series with cerebellar ataxia and seizures, MRI brain was normal.

Metronidazole neuropathy is due to the overdose of the drug. Out of ten patients, only seven visited on follow-up. Four had had recovered in 3 months time. Other three had improved with some residual sensory disturbances. Cerebellar ataxia patient had completely recovered on follow up. A complete recovery is usual in metronidazole peripheral neuropathy. Recovery time depends on the dose and severity of neuropathy. Recovery was seen in 1 month in one patient reported elsewhere after discontinuing metronidazole.[1]

CONCLUSION

The patients on metronidazole need to be monitored closely for neurotoxicity. The patients have to be educated for not continuing metronidazole indefinitely based on ultrasound abdomen findings. When the symptoms appear early, dose of the medications has to be reduced. In addition, total dose of metronidazole should not exceed 42 g.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Koul R, Shasthry SM, Ramalingam A, Sarin SK. Metronidazole-related neurotoxicity in a referral hospital. Indian J Med Sci 2021;73(2):217-20.