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Metronidazole-Induced Neurotoxicity: A Rare Case Report

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Abstract **Case Report**

***Introduction*:** Metronidazole, a commonly used nitroimidazole antibiotic, is associated with various side effects, including neurological complications such as toxic peripheral neuropathy, cerebellar dysfunction, and seizures. Despite its widespread use, serious neurological effects can occur, necessitating prompt diagnosis and discontinuation of treatment. ***Observation*:** We present the case of a 26-year-old patient with colonic Crohn's disease treated with metronidazole, who experienced both central and peripheral neurotoxicity after a cumulative exposure of 42 days. The patient presented with convulsive seizures and paresthesia of the lower limbs, prompting a comprehensive etiological work-up, including metabolic assessments, imaging studies, and lumbar puncture. The absence of abnormalities in diagnostic tests, coupled with symptom improvement upon discontinuation of metronidazole, led to the diagnosis of metronidazole-induced neurotoxicity. ***Discussion*:** Metronidazole-induced neurotoxicity is a known but underreported complication, affecting both the central and peripheral nervous systems. The duration of treatment before symptom onset can vary, and the association of central and peripheral symptoms is rare. Radiological findings, often observed on T2-weighted MRI, may show characteristic lesions, but their absence does not exclude the diagnosis. The pathogenesis involves metronidazole's ability to cross the blood-brain barrier, leading to the generation of superoxide radicals and axonal swelling. Prompt recognition and discontinuation of metronidazole are crucial for potential symptom resolution. ***Conclusion*:** This case underscores the importance of considering metronidazole-induced neurotoxicity in patients presenting with neurological symptoms during or after metronidazole treatment. A high clinical suspicion, coupled with a detailed evaluation and, if needed, discontinuation of metronidazole, is vital for timely diagnosis and management. Recognition of this complication can prevent long-term neurological deficits and contribute to safer antibiotic usage.

Keywords: Metronidazole, nitroimidazole antibiotic, neuropathy.

INTRODUCTION

Metronidazole is a nitroimidazole antibiotic, commonly used in the treatment of infections caused by anaerobic bacteria or protozoa. It often causes side effects such as nausea, headache and a metallic taste in the mouth; however, higher doses and/or prolonged use can lead to serious neurological effects, including toxic peripheral neuropathy, cerebellar dysfunction, visual impairment, vestibular toxicity, cochlear toxicity, ataxia, dysarthria or seizures [1]. The time of onset of these effects can vary from a few days to a few weeks, and also depends on the cumulative dose of metronidazole. In a case-control study, the incidence of neurological side effects was 0.25%, but this is probably an underestimate [1]. A strong clinical suspicion and a detailed neurological evaluation are necessary to make the diagnosis in time, as it may be reversible.

We report a case of metronidazole-induced neurotoxicity, affecting both the central and peripheral nervous systems, reversible after discontinuation of treatment.

CASE DESCRIPTION

A 26-year-old patient with colonic Crohn's disease with anoperineal lesions who was admitted to our department for perineal abscesses. A pelvic MRI revealed complex active perianal fistulas, complicated by a right gluteal collection measuring 43x17 mm. The patient had surgical drainage in addition to intravenous (IV) bi-antibiotherapy with ciprofloxacin (400 mg twice daily) and metronidazole (500 mg 3 times daily). After three weeks of parenteral treatment, he was switched to oral therapy (ciprofloxacin + metronidazole) for a further three weeks and discharged.

However, two weeks later, the patient presented again with insomniac proctalgia and purulent anal discharge secondary to a recurrence of perianal collection. He was hospitalized for parenteral antibiotic therapy (Ceftriaxone 2g/d with metronidazole 500 mg 3 times daily) and a second surgical drainage.

One week after hospitalization, the patient presented three convulsive seizures: two generalized tonic-clonic seizures and one partial seizure with tremors of the hemiface, associated with bilateral paresthesia of the lower limbs.

The etiological work-up consisted of metabolic analyses and lumbar puncture; a cerebral CT scan in search of a cerebrovascular accident, a cerebral angio-MRI for thrombophlebitis; and an electroencephalogram, which all returned normal.

Given the negativity of the entire etiological work-up, we were able to rule out differential diagnoses and thus incriminate metronidazole, especially in view of the improvement in paresthesia after changing antibiotic therapy, which was adapted to the cytobacteriological examination of the pus sample, and the absence of any recurrence of seizures.

The abscess clearly regressed under ceftriaxone.

The patient showed no neurological signs after discontinuation of metronidazole. He was discharged home which physical therapy and continued to be followed up in consultation. After one month, the paresthesia disappeared and he no longer needed physiotherapy.

DISCUSSION

One of the most widely used antibiotics, metronidazole is likely to cause serious neurological side-effects, both in the short and long term.

The first case of metronidazole-induced neurotoxicity was reported in 1977 in a 19-year-old woman.

Numerous case reports have subsequently been published. In a systematic review of 136 cases of metronidazole-induced neurotoxicity, the duration of treatment before onset of central nervous system dysfunction ranged from 14 to 52.5 days [2]. In our case, it was 42 days. Of the 136 patients reported in this systematic review, 119 had partial or complete resolution of symptoms after discontinuation of treatment. 12 of the 136 patients had an unfavorable course, including persistent significant neurological deficits and death. However, these 12 patients had previous comorbidities, including organ failure or malignancy [2].

Case reports suggest that it can take an average of 6-7 weeks for symptoms to appear. However, symptoms may also appear a few days after the start of treatment [3, 4].

In our case, symptoms appeared after 6 weeks of metronidazole, which is consistent with literature data.

Metronidazole affects both the central and peripheral nervous systems. In the peripheral, it causes slowly progressive symmetrical distal sensory-motor polyneuropathy with paresthesia. In the central nervous system, it causes encephalopathy and cerebellar dysfunction, with dysarthria, ataxia, dysmetria and nystagmus.

The association of both central and peripheral symptoms is rare [4], which is our patient's case; who presented seizures and paresthesia of the lower limbs.

Up to 90% of patients with central nervous system involvement show characteristic lesions on magnetic resonance imaging (MRI).

Typical radiological signs are most often observed on T2-weighted MRI, in FLAIR (fluid-attenuated inversion recovery) sequence. The abnormalities often present are symmetrical hyperintense lesions in the serrated nuclei, with occasional lesions in the splenium of the corpus callosum and the dorsal part of Varole's bridge emitting the same types of characteristic signals.

These radiological lesions generally regress after discontinuation of metronidazole, although peripheral neuropathy may persist [2-9].

The differential diagnosis of MRI findings includes demyelinating diseases and metabolic, infectious and inflammatory processes [9].

However, these lesions are not mandatory for diagnosis, which relies mainly on strong clinical suspicion, elimination of differential diagnoses, and improvement of clinical signs after discontinuation of metronidazole. In our case, the MRI showed no anomaly. The diagnosis was made after eliminating all the differential diagnosis based on the metabolic workup, the lumbar puncture; the cerebral CT scan, the cerebral angio-MRI and the electroencephalogram which all returned normal.

Two-thirds of patients suffering from central nervous system dysfunction attributable to metronidazole improve after stopping the drug. In our case, paresthesia disappeared gradually after stopping metronidazole. After 3 weeks, the patient had no signs of paresthesia and he didn't have any seizure.

The pathogenesis of this toxicity remains poorly understood. Metronidazole readily crosses the blood-brain barrier, and its intermediate metabolites bind to the DNA and RNA of neuronal cells, inducing the

generation of superoxide radicals that cause axonal swelling [4].

Another important theory is that axonal swelling is caused by vasogenic edema, possibly due to altered vitamin B1 activity, given the conversion by metronidazole of a thiamine analogue in vivo.

Patients taking metronidazole for inflammatory bowel disease, osteomyelitis or large, undrained abscesses are at greater risk of neurotoxicity, due to the generally long duration of exposure. A review of 110 cases of metronidazole-induced encephalopathy in adults showed that a median cumulative dose of 65.4 g is likely to cause this toxicity, but there was considerable variability (5-2000 g) [3].

Studies have shown that treatment with corticosteroids can accelerate healing, perhaps due to the vasogenic edema that contributes to the neurotoxicity of metronidazole [5].

CONCLUSION

A strong clinical suspicion is required to diagnose these cases, especially when patients present with neurological symptoms of recent onset after initiation of metronidazole. MRI remains an important tool, even though it may be normal in 10% of cases. In case of doubt, it is preferable to stop metronidazole and switch to another antibiotic, in order to observe improvement and incriminate the drug.

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