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Psychotic mania induced by metronidazole: A rare case of antibiomania

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Summary

Metronidazole, a widely used antimicrobial agent, has been associated with rare neuropsychiatric adverse effects, including antibiotic-induced mania (antibiomania). We report the case of a 46-year-old woman with a history of bipolar disorder type I, previously triggered by antidepressant treatment, who presented with an acute onset of a manic episode with psychotic features following prolonged metronidazole treatment. The patient had remained euthymic and medication-free for approximately nine years prior to this episode. Metronidazole was discontinued upon admission, and appropriate psychiatric treatment was initiated. Manic and psychotic symptoms resolved completely within three days, supporting a probable causal association. This case highlights the potential of metronidazole to induce manic episodes, particularly in individuals with a predisposition to mood disorders, and aims to discuss the possible underlying mechanisms through which metronidazole may contribute to the development of mania.

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INTRODUCTION

Bipolar disorder is a chronic and serious disorder characterized by recurrent episodes of depression and mania/hypomania, with patients being either asymptomatic or experiencing subthreshold symptoms between episodes. This disease can occur spontaneously or sometimes it can be triggered by different reasons such as medical conditions, medications or substances. It has been suggested that drug-induced manic episodes are more likely to occur in people who are predisposed to mood disorders (Jimenez-Fernandez et al., 2021; Kivlichan et al., 2024; Peet & Peters, 1995). Among the causes of drug-induced mania, many drugs, especially antidepressants, corticosteroids, levodopa, sympathomimetic amines, iproniazid, thyroxine, captopril, etc. have been reported to date (Puri et al., 2021). Antibiotics are also noteworthy in this regard due to their widespread use and rare but sometimes serious psychiatric side effects. There are case reports in the literature regarding manic reactions triggered by antibiotics such as clarithromycin, ciprofloxacin, amoxicillin-clavulanic acid, metronidazole, erythromycin, isoniazid, ofloxacin, etc. and this syndrome has been termed 'antibiomania' (Abouesh et al., 2002; Althubyani et al., 2024). Although antibiotics have psychological and neurological side effects, few of these affected patients are seen by psychiatrists. In this article, it is aimed to report a bipolar disorder diagnosed patient who developed a new manic episode induced by metronidazole and to discuss the possible etiopathogenetic mechanisms that may underlie this episode.

CASE REPORT

A 46-year-old female patient presented to the emergency department due to an increase in the rate and amount of speech, irritability, decreased need for sleep, increased energy and activity, uncontrolled spending of money, ideas of reference, persecutory and grandiose delusions, disorganized behavior and speech, agitation, and partial impairment in time orientation. These symptoms started suddenly and increased rapidly within two days. As a result of the obtained information, it was learned that the patient's first psychiatric symptoms occurred after the traffic accident she had in 2002. She was diagnosed with post-traumatic stress disorder, treated with citalopram for 6 months and then she recovered. She did not have any psychiatric symptoms until 2010, but developed depressive symptoms secondary to psychosocial stressors in 2010. She started to receive fluoxetine 20 mg/day. In the second week of fluoxetine treatment, she experienced symptoms such as increased talking, distraction, increased activity and energy, decreased need for sleep, identifying new areas of interest and projects, and grandiose delusions. She was admitted to the psychiatric inpatient unit with the diagnosis of bipolar disorder type I, manic episode with psychotic features. Her treatment was prescribed as olanzapine 20 mg/day and clonazepam 2 mg/day. In the second week of treatment, mania symptoms completely regressed and she was discharged euthymic. During the follow-up, treatment was switched from olanzapine to valproic acid due to sedation and weight gain. The patient was euthymic with valproic acid 1000

mg/day treatment for approximately 3 years. In 2014, the patient's treatment was terminated under the supervision of a doctor because of pregnancy planning. She had not experienced any mood episodes and had not used psychotropic medication since 2014.

After applying to the emergency room in October 2023, the patient was admitted to the psychiatric service for the second time with the diagnosis of bipolar disorder type I, manic episode with psychotic symptoms. The Young Mania Rating Scale (YMRS) score during admission to the psychiatric inpatient unit was determined as 35. Because of excitation and poor treatment adherence, the patient was administered zuclopenthixol acuphase 50 mg 1*1 intramuscular twice and haloperidol 5 mg 1*1 intramuscular once in total. The patient became sedated after these parenteral treatments.

During her hospitalization, it was learned that she was receiving regular antibiotics for the last 4 months due to the infection of the maxillary implant that applied after the traffic accident she had in 2002 and the development of gingivitis. Because of this infection, amoxicillin-clavulanic acid 1000 mg/day treatment was prescribed to her for approximately 2.5 months. No psychiatric symptoms occurred during the use of amoxicillin-clavulanic acid. Amoxicillin-clavulanic acid treatment was switched to metronidazole 1.5 months ago. When the patient was admitted, she was still continuing the treatment at the same dose. Metronidazole antibiotic therapy was discontinued on the first day of the hospitalization, because it was no longer indicated.

The patient was diagnosed with hypertension and hypothyroidism. She has been stable for a long time with the treatment of levothyroxine 100 mcg/day for hypothyroidism and lisinopril 20 mg-hydrochlorothiazide 12.5 mg/day for hypertension. She is an active smoker of 10 cigarettes/day and does not use alcohol or any substances.

Laboratory examinations revealed hyponatremia (Na: 131 mmol/L), hypokalemia (K: 3.0 mmol/L), increased C-reactive protein (CRP: 11 mg/L) and increased creatine kinase (CK: 826 U/L). Erythrocytes, leukocytes and bacteria were observed in the complete urine analysis. All substances were detected negative in the 5-substance screening test in urine. According to the nephrology consultation, hyponatremia and hypokalemia were associated with the patient's consumption of approximately 5–6 liters of water per day over the previous two days and were considered dilutional. The patient was subjected to fluid restriction and potassium effervescent tablets were applied orally for 2 days. A single dose of fosfomycin sachet was administered for urinary tract infection with the recommendation of infectious diseases department. In addition, topical treatment with fusidic acid 2% cream was applied twice a day to the bullous infected lesions observed on the patient's feet. After these treatments, all the patient's physical symptoms became stable. It was thought that the CK elevation was related to the injections and physical restraint during agitation. During routine follow-up, CK values decreased within the reference range in a short time. Computed tomography (CT) of the brain was normal. No pathology was detected in brain magnetic resonance imaging (MRI), except for a few millimetric chronic ischemic changes in the subcortical white matter in the supratentorial region.

After discontinuation of metronidazole and administration of parenteral antipsychotic treatments, the patient's psychiatric symptoms completely regressed on the 3rd day of treatment. Valproic acid 750 mg/day was initiated for bipolar disorder prophylaxis. After the valproic acid blood level stabilized in the range of 50–100 μg/mL, the patient was discharged euthymic on the 20th day of hospitalization.

DISCUSSION

To date, side effects of various antibiotics on the central nervous system (CNS) have been reported in the literature (Althubyani et al., 2024). Dizziness, tremors and hallucinations are the most common neurologic and psychiatric adverse events and occur in 9-11% of patients on an antibiotic treatment (Khandheria et al., 2014). Antibiotic-induced manic episodes are observed much less frequently than other psychiatric side effects and the information is restricted to a limited number of case reports. In a review including unpublished cases by the World Health Organization (WHO) and the Food and Drug Administration (FDA), it was reported that clarithromycin was associated with antibiotic-induced mania at the highest rate (27.6%), with a total of 23 cases. Ciprofloxacin (14.4%), ofloxacin (12%), cotrimoxazole (7.3%), erythromycin (6%), isoniazid (6%) and metronidazole (6%) are among other related antibiotics, respectively. Some commonly prescribed antibiotics, such as norfloxacin, ampicillin, amoxicillin-clavulanic acid, etc., have been found to be associated with mania at rates lower than 5% (Abouesh et al., 2002). The fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has listed antibiotic use as a causative factor for secondary mania (AlShakori et al., 2022).

Antibiotic-triggered mania generally has characteristics such as acute onset, rapid limitation when medication is discontinued, temporary nature and recurrence when

medication is restarted. It has been stated that neurotoxicity-related symptoms occur typically after prolonged use but also at low cumulative doses too (Parker & Russo, 2025; Puri et al., 2021). The time before the onset of neuropsychiatric symptoms is usually longer than the resolution of symptoms (Neufeld et al., 2017). Reports to date indicate that antibiotic-related manic reactions were most frequently observed between the ages of 31-50 (49%) and women were more affected than men (57.6%) (Abouesh et al., 2002).

Metronidazole is known to have CNS side effects such as paresthesia, cerebellar symptoms, syncope, confusion, psychosis, encephalopathy, etc. Metronidazole-induced mania is very rare, the number of cases reported in the literature is less than 10 and the mechanisms by which it causes mania are unclear (Puri et al., 2021). Metronidazole can cross the blood-brain barrier. Preliminary findings suggest both direct, i.e. toxic and indirect CNS effects (Ahmed et al., 1995). Although the reported incidence of metronidazole-induced neurotoxicity is approximately 0.25%, this is likely an underestimate. Mechanisms such as free radicals and protein synthesis inhibition mediated nerve fiber damage, axonal degeneration, competitive-reversible monoamine oxidase (MAO) inhibition and associated dopamine increase, aberrant γ-amino butyric acid (GABA) signaling have been proposed for metronidazole-induced mania (Parker & Russo, 2025). However, it has been suggested that mechanisms related to cortisol, prostaglandins, and the gut–brain–microbiota axis should be taken into consideration in future studies (AlShakori et al., 2022; Befani et al., 2001; Dinan & Dinan, 2022; Puri et al., 2021). The onset of symptoms due to metronidazole, which has a half-life of 8 hours, varies from a few days to 6-7 weeks. According to the reports, the dose of metronidazole varies between 250-2000 mg/day and the method of administration is oral or parenteral. In our case, the emergence of manic symptoms later than the first 10 days generally stated in the literature was thought to be related to long-term oral use of metronidazole at a lower dose of 500 mg. Because its half-life is short, symptoms usually decrease rapidly within about 3 days after discontinuation (AlShakori et al., 2022). In our case, it was observed that psychiatric symptoms regressed faster than expected after short-term parenteral antipsychotic administration and discontinuation of metronidazole.

In the last case reported in 2023, a manic episode with psychotic features that occurred with metronidazole 1000 mg/day treatment was documented in a female patient who was diagnosed with bipolar disorder after a manic episode triggered by antidepressant use in the past. After stopping metronidazole, the patient started to recover on the second day of 5 mg/day olanzapine treatment (Chan, 2023). In our case, it was thought that her condition was a manic episode triggered by metronidazole because bipolar disorder was diagnosed initially after antidepressant use in the past, she remained stable for a long time without medication, psychiatric symptoms re-emerged after metronidazole treatment was started and rapidly recovered after drug discontinuation.

CONCLUSION

Drug-disease interactions as well as drug-drug interactions should be taken into consideration during the treatment processes of patients. The incidence of antibiotic-induced mania needs to be determined in the future. There is a need for studies that can reveal the relationship between factors such as drug dosage, style of administration, treatment duration, and psychiatric symptoms. It is crucial to notice all causes of mania, including antibiotics in acute presentations.

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