Autism, pain, and the NMDA receptor

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Ms. G, a 36-year-old woman, presented to the emergency department (ED) requesting a neurologic evaluation. She told clinicians she had "NMDA receptor encephalitis."

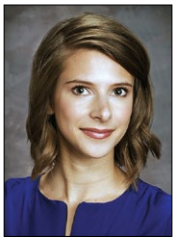
Ms. G reported successful self-treatment of "life-long" body pain that was precipitated by multiple external stimuli (food, social encounters, interpersonal conflict, etc.). Through her own research, she had learned that both ketamine and magnesium could alter nociception in rats through *N*-methyl-D-aspartic acid (NMDA) receptor antagonism, and so she decided to try treating her pain with Delsym, an over-the-counter cough syrup containing dextromethorphan polistirex (DXM), which at high doses acts as an NMDA receptor antagonist. She said she was taking Delsym, 120 mg/d, and magnesium oxide, 600 mg/d.

In the ED, Ms. G had a labile affect, pressured speech, and flight of ideas. She denied any history of psychiatric treatment, suicide attempts, or substance abuse. Ms. G's family reported she had been unusually social, talkative, and impulsive. She was admitted to the inpatient psychiatric unit with a diagnosis of mania.

On psychiatric evaluation, Ms. G was grandiose, irritable, and perseverative about her aberrant symptoms. She felt she did not experience the world as other people did, but found relief from her chronic pain after taking Delsym. She was not taking other medications. Ms. G did not report a family history of bipolar disorder or psychosis. Her laboratory results, including a comprehensive metabolic panel, complete blood count, lipid panel, thyroid studies, urine drug screening, and urinalysis, were unremarkable. Her blood pressure was mildly elevated (141/82 mm Hg).

Ms. G's eventual diagnosis was substance-induced mania (DXM). The DXM-containing cough syrup and magnesium were discontinued in the hospital. She was stabilized on lithium extended-release, 900 mg/d (blood level 0.8 mmol/L), and olanzapine, 10 mg/d at bedtime. However, after discharge, Ms. G resumed using Delsym, which resulted in 3 subsequent psychiatric hospitalizations for mania during the next year.

I first treated Ms. G as an outpatient after her second hospitalization. At that point, she was stable. Her mental status was calm and cooperative, and she had a linear thought process. At her baseline, in the absence of mania, she had a blunted affect. She understood that DXM caused her to have manic symptoms, but she continued to believe that Delsym and magnesium cured her physical suffering and social inhibition. I noticed Ms. G would use figurative language inappropriately. I later learned she had sensitivities to food textures and a specialized interest in electronics. Because of this, I suspected Ms. G was on the autism spectrum; she met several DSM-5 criteria



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for autism spectrum disorder (ASD), particularly deficits in social-emotional reciprocity, highly restricted interests, and hyperreactivity to sensory input.

Upon routine lab screening, Ms. G was found to have hypothyroidism, with a thyroid-stimulating hormone level of 6.67 mcIU/mL. This resolved after discontinuing lithium. Olanzapine caused adverse metabolic effects and also was discontinued. Ms. G remained euthymic without any mood-stabilizing medication, except during periods when she abused DXM, when she would again become manic. Eventually, her motivation to avoid hospitalization would promote her abstinence.

Implications of NMDA receptor antagonism

The use of ketamine as an NMDA receptor antagonist for treating depression and other psychiatric illnesses has gained momentum. Esketamine, the S-enantiomer of racemic ketamine, is now available as an FDA-approved intranasal formulation for treatment-resistant depression. Ketamine stops afferent nociception to the brain and is used as an analgesic (at low concentrations) and anesthetic (at high concentrations).[1]

Dextromethorphan is abused as a recreational drug because at high doses it works similarly to both ketamine and phencyclidine. Individuals who abuse DXM can develop psychosis, motor/cognitive impairment, agitation, fevers, hypertension, tachycardia, and death.[2] In patients with ASD, researchers have identified genetic variations of NMDA receptors that are linked to dysfunction of these receptors.[3] In animal models, as well as in humans, researchers have found that suppression or excitation of the NMDA receptor can ameliorate ASD symptoms, including social withdrawal and repetitive behaviors.[3]

Many individuals with ASD suffer from sensory abnormalities, including a reduced sensitivity to pain or a crippling sensitivity to various stimuli. Patients with ASD may have difficulty describing these abnormalities, and as a result, they may be misdiagnosed. One case report described a 15-year-old girl diagnosed with social anxiety and chronic generalized pain when in social situations.[4] Pediatric rheumatologists had diagnosed her with "amplified pain syndrome." When she presented to a mental health clinic for a neurodevelopmental evaluation, she explained to clinicians how she simply "did not 'get' people; they are just empty shells" and subsequently was given a diagnosis of ASD.[4]

In psychiatric patients who have comorbid substance use disorders, it is vital for clinicians to not only detect the presence of substance misuse, but also to understand what drives the patient toward abuse. Ms. G's case, with its combination of substance abuse and ASD, illustrates the importance of listening to our patients for more precise diagnostic formulations, which then shape our treatment recommendations.

Clinical Point

Ms. G's case illustrates the importance of listening to our patients for more precise diagnostic formulations

References

1. Vadivelu N, Schermer E, Kodumudi V, et al. Role of ketamine for analgesia in adults and children. J Anaesthesiol Clin Pharmacol. 2016;32(3):298-306.
2. Martinak B, Bolis R, Black J, et al. Dextromethorphan in cough syrup: the poor man's psychosis. Psychopharmacol Bull. 2017;47(4):59-63.
3. Lee E, Choi S, Kim E. NMDA receptor dysfunction in autism spectrum disorders. Curr Opin Pharmacol. 2015;20:8-13.
4. Clarke C. Autism spectrum disorder and amplified pain. Case Rep Psychiatry. 2015;2015:930874. doi: 10.1155/2015/930874.