A Possible Role for *Uncaria tomentosa* (cat's claw) in a Case of Serotonin Syndrome

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Serotonin syndrome is caused by elevated levels of serotonin and overstimulation of serotonergic neurons.[1] This serotonin excess may be caused, singularly or in combination, by agents that enhance serotonin synthesis (eg, L-tryptophan), increase serotonin release (eg, amphetamine, dextromethorphan, lithium), stimulate serotonin receptors (eg, buspirone, trazodone), inhibit serotonin catabolism (eg, linezolid), or inhibit serotonin reuptake (eg, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mirtazapine, tramadol).[2] The incidence is unknown. Common clinical presentations include agitation, autonomic dysfunction, gastrointestinal symptoms, hyperthermia, tremors, hyperreflexia, clonus, delirium, and sometimes death.[2] The Hunter criteria,[3] which are often used to make the diagnosis of serotonin syndrome, require the ingestion of a serotonergic drug along with clonus, agitation, autonomic disturbance, tremors, or hyperreflexia.[1] In milder cases, symptoms frequently resolve with discontinuation of serotonin-enhancing medications along with supportive care including benzodiazepines for agitation; however, severe cases may require more intense treatment such as serotonin antagonists (cyproheptadine), neuromuscular paralysis, intubation, and mechanical ventilation.[1,4]

Case Report

A 37-year-old woman with a history of gastroesophageal reflux disease, hyperlipidemia, vertigo, headaches, anxiety, and depression presented to the emergency department for evaluation of acute onset of confusion, visual distortions, derealization, and worsening symptoms of anxiety. It was noted that 6 weeks prior, the patient's medications had changed from citalopram 40 mg daily and bupropion SR 150 mg twice daily to fluoxetine 40 mg daily. Metoclopramide 5 mg 4 times daily as needed had been added 4 weeks prior to presentation and dextrobrompheniramine/phenylephrine 2 weeks prior. She also had a prescription for tramadol, which she "hadn't used in months." She denied alcohol or other substance use. Her vital signs were temperature: 37°C (98.6°F), blood pressure: 124/80 mm Hg, heart rate: 102 bpm, and respiratory rate: 18 breaths/minute. The physical examination revealed significant tachycardia, hyperreflexia, clonus, and restlessness but was otherwise unremarkable including the remaining neurologic examination. Laboratory studies showed a mildly elevated white blood cell count of $12.4\times10^3/\mu L$ and an elevated platelet count of $403\times10^3/\mu L$. The comprehensive metabolic panel was significant only for elevated blood glucose of 119 mg/dL. Thyroid testing was within normal limits, and urine drug screen was positive for benzodiazepines (which were prescribed). A head computed tomography scan was normal. An electrocardiogram showed a prolonged QTc of 480 ms but was otherwise normal. While in the emergency department, she received a fluid bolus of 1,000 mL of normal saline as well as 2 mg of intravenous lorazepam for severe anxiety.

Psychiatric evaluation revealed the patient to be highly anxious and tearful with a dysphoric affect. She had begun to feel "strange" approximately 3 weeks prior, seeking help from her primary care provider for dizziness and diagnosed with sinusitis and vertigo. The patient reported acute worsening of these symptoms 48 hours prior to presentation. She described acute confusion, disorientation, and visual disturbances of "double vision" and "everything looking distorted and in high definition." She also reported racing, bizarre thoughts. Physical symptoms over the same time period included intermittent flushing, tachycardia, and episodes of sweating.

Further review revealed that around the time of onset of these recent acute symptoms, the patient had begun an intensive weight loss routine (which she referred to as a ketone "reboot") that included over-the-counter supplementation with a proprietary blend of nutraceuticals purported to induce ketosis, a metabolic state achieved through prolonged low blood glucose availability and a corresponding increase in ketone bodies in the blood and urine. The herbal supplement *Uncaria tomentosa* was noted to be present in each of the supplements she took for about 48 hours in place of eating her normal diet.

At admission for suspected serotonin syndrome, all psychiatric medications were held, and benzodiazepines were added for anxiety as needed. She showed prompt improvement with supportive care. Treatment recommendations included holding psychiatric medications for a 2-week washout period

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and cessation of over-the-counter dietary supplements. The patient was discharged 2 days later and scheduled for a follow-up with her primary care physician.

Discussion

In the weeks leading up to her admission, this patient's medication regimen contained a number of agents that might increase serotonergic tone. Fluoxetine, tramadol, and the prokinetic drug metoclopramide are known contributors to serotonin overload, while bupropion has been singled out as a causative agent in some instances of serotonin syndrome.[5] Interestingly, brompheniramine has been listed as a drug with serotonin reuptake inhibitory properties,[6] though it is unclear whether dexbrompheniramine shares this property.

Of particular interest, our patient also began an intensive weight loss diet regimen several days prior to admission, which for about 48 hours consisted only of 5 over-the-counter formulations, each containing *Uncaria tomentosa*, and coinciding temporally with an escalation in her presenting symptoms. *Uncaria tomentosa* (also known as cat's claw or una de gato) is a large, woody vine in the Rubiaceae family that is indigenous to the Amazon rainforest and has been used medicinally by Peruvian natives for centuries.[7] *Uncaria tomentosa* extracts have been used traditionally to treat allergies, arthritis, inflammation, rheumatism, and cancer among other ailments. Popular media sources tout the extract as a treatment for hypertension, arthritis, allergies, cold sores, and abdominal cramps and to prevent viral infections and tumor growth. Some diet preparations, such as that of our patient, may contain *Uncaria tomentosa* purporting to enhance DNA repair.

While there are a number of in vitro and animal studies suggesting that *Uncaria tomentosa* may have bona fide anti-inflammatory and immune-modulating effects, including a theoretical impact on the severe acute respiratory syndrome coronavirus 2 virus,[8] there are limited clinical studies in humans. These studies addressed the extract's efficacy against cancer, HIV, Alzheimer's disease, rheumatoid arthritis, and herpes simplex and were recently reviewed by the European Medicines Agency,[9] which concluded that the data are insufficient to support the efficacy of *Uncaria tomentosa* in the treatment of any of these illnesses.

Nonetheless, *Uncaria tomentosa* extracts or decoctions have demonstrated a number of biologically active oxindole alkaloids thought to be responsible for its putative medicinal activity. Several studies in animal models have suggested a role for 1 or more of these alkaloids in increasing serotonin levels or modulating serotonin receptor activity.[10–13] Our review of the other ingredients in our patient's dietary supplements found several with at least some data to suggest a role in serotonin modulation, but only 2 with direct evidence of lowering (taurine) or increasing (bioperine/piperine) serotonin. These ingredients appeared in only 1 supplement each, as opposed to *Uncaria tomentosa*, which was contained in all 5 supplements.

Perhaps the patient's medications listed previously, in various combinations over the previous 3 months, account for her early symptoms. Although it cannot be proven, our hypothesis is that, to this pharmacologic background, the patient added 48 hours of an intensive nutritional supplement regimen with several products, all of which contained *Uncaria tomentosa*, perhaps further increasing her serotonergic load, resulting in a fully apparent serotonin syndrome as described here. Whether this presumptive increase in serotonin load was due to a direct result of the pharmacodynamic or pharmacokinetic properties of *Uncaria tomentosa* is, of course, unknown.

Conclusion

This is the first report, to our knowledge, suggesting a role for *Uncaria tomentosa* in the etiology of a case of serotonin syndrome. Clinicians will always do well to assess patients' use of over-the-counter remedies, including nutritional supplements. In cases of suspected serotonin syndrome, specific questions regarding *Uncaria tomentosa* consumption may be prudent.

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