Isolated Oculogyric Crisis on Clozapine Discontinuation

SIR: It is now well known that an abrupt discontinuation of clozapine leads to a discontinuation syndrome characterized by autonomic, behavioral, motor, and psychotic symptoms.[1] We report a case of an isolated oculogyric crisis in a patient who stopped taking clozapine, and discuss the unique nature of this presentation and the putative mechanism of motor symptoms associated with clozapine discontinuation.

Case Report

"Ms. A," an 18-year-old adolescent, was diagnosed with mild mental retardation with behavioral problems, the latter including aggressive and violent behavior, disorganized speech, and disrupted biological functions. She had no history of psychiatric illness. Two months after the onset of these symptoms, she was started on a regimen of haloperidol (up to 10 mg/day), but developed extrapyramidal symptoms which were treated with trihexyphenidyl, 4 mg/day. There was no history of dystonias or dyskinesias on haloperidol. However, as the patient developed akathisia and there was no improvement in symptoms despite being treated with these medications for 5 weeks, both haloperidol and trihexyphenidyl were stopped. Ms. A remained drug-free for the next 3 weeks and was subsequently started on a regimen of clozapine, 25 mg/day, titrated to 300 mg at bedtime over a period of 4 weeks. Her behavioral symptoms showed remarkable improvement with clozapine. Six weeks after commencing clozapine, she inadvertently ran out of her supply of this medication and could not get it refilled on time. Within 48 hours after her last dose, she developed an acute oculogyric crisis. This was characterized by uprolling of the eyeballs lasting for 60–90 minutes at a time and recurring every 2 to 4 hours. The patient immediately consulted her treating psychiatrist, and clozapine was reinstated at its original dose, resulting in dramatic resolution of the oculogyric crisis. During this whole time, no dystonias or dyskinesias in other parts of the body were observed and there was no evidence of nausea, vomiting, diarrhea, perspiration, palpitations, or restlessness. No deterioration in behavioral symptoms was reported. Her neurological examination results, other than the aforementioned focal dystonia, were unremarkable and so were the results of a head computed tomography (CT) scan.

Comment

This case provides some unique insights into our understanding of the mechanism of discontinuation-emergent movement disorders with clozapine. This patient had no prior history of neuroleptic-induced dystonia or dyskinesia, and the speculation that clozapine discontinuation may have led to reemergence of these movement disorders may not be valid in this case. In addition, this patient exhibited oculogyric crisis, whereas other investigators have reported mainly limb-axial and neck dystonia/dyskinesia with clozapine discontinuation.[1] Cholinergic rebound has been hypothesized to be responsible for the symptoms associated with clozapine discontinuation.[2] Moreover, reports of cholinergic excess in patients on cholinesterase inhibitors, leading to acute dystonia, further support the putative role of cholinergic rebound in the emergence of dystonias on clozapine discontinuation.[3] However, if this were the sole mechanism, our patient would have exhibited other peripheral signs and symptoms of cholinergic withdrawal. In line with this, cholinergic rebound occurs after chronic cholinergic blockade, and our patient had been treated with clozapine for only 6 weeks, which may not be sufficient to cause supersensitivity of the muscarinic receptors. Animal studies have shown that M4 muscarinic receptors exert an inhibitory effect over striatal D1 dopamine receptor-mediated locomotor stimulation.[4] Thus, it can be hypothesized that the removal of this muscarinic inhibition of the dopaminergic system in the striatum as a result of clozapine discontinuation may result in functional dopaminergic supersensitivity, manifesting as movement disorders. This suggests that besides cholinergic supersensitivity, other neurotransmitters also may play a part in the emergence of motor symptoms following clozapine discontinuation. Further research in this realm is encouraged.

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A Case of Difficult Diagnosis of Rabies in the Absence of a Dog Bite in a Patient With Depression

SIR: Symptoms characteristic of rabies are hydrophobia, agitation, and irritability. Some cases present with depressive symptoms frequently termed as "silent rabies." History of contact with a diseased animal is usually available for a diagnosis of rabies. In the absence of history and classical symptoms, rabies may be missed in the differential diagnosis.

Case Report

A 46-year-old man was brought into the emergency room by his wife at around 11 p.m. At the time of presentation he had a melancholy look on his face and was heaving and hyperventilating at irregular intervals. History revealed that he had been receiving treatment for depression as a consequence of business loss a few months back. He was known to have mood swings and to fluctuate between states of depression and anxiety. Since his business loss, he had been taking amitriptyline. His wife explained that his depression had increased after his dog died 10 days before. The patient made no mention of any untoward symptoms in the dog that could have resulted in its death. The patient's appetite and food intake had decreased, but were adequate. He had no history of any other significant medical conditions. He was admitted for observation and given alprazolam, 0.25 mg, with a provisional diagnosis of anxiety. A psychiatric consultation was arranged for the next day. Blood samples were sent for CBC, blood glucose, and electrolytes.

At around 2 a.m. on the same night his wife called us to see him. His hyperventilation had increased and he appeared restless and irritated. His laboratory test results were within normal range. We started an intravenous line and he was given 2 mg of lorazepam. Because his hyperventilation continued unabated, we transferred him to the intensive care unit. An emergent opinion was sought from a neuropsychiatrist, who suspected rabies. To confirm diagnosis, we ordered a lumbar puncture and skin biopsy. We started him on human cell diploid vaccine; and gave him 1 ml in the deltoid. Family members were also started on prophylactic immunization. He had no bite marks, so a local vaccination was not considered. He was transferred into isolation, but despite all of our supportive measures, he died 2 days after admission. Results that were available, meanwhile, showed the presence of antibodies for rabies in the spinal fluid and presence of the rabies antigen in the skin biopsy.

Discussion

This patient presented with hyperventilation, which is commonly seen in patients with anxiety and a history of depression. The nature of presenting symptoms and history had favored the initial diagnosis of a state of anxiety and depression. The death of the patient's dog was viewed as one of the compounding factors rather than as a triggering factor. The absence of classical symptoms like hydrophobia and opisthotonus in this patient further prevented an initial straightforward diagnosis of rabies.

Rabies is a zoonotic disease caused by lyssavirus and human infection by the rabies virus and usually occurs as a result of a bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes into contact with the victim's mucosa or fresh skin lesions or on very rare occasions through inhalation of virus-containing aerosol. In this case, the route of transmission is unknown but probably due to the latter two reasons.

The virus first binds to receptors on the muscle cells, resulting in mild fever and pain. This patient had no history of fever or pain. The virus later affects the nerves, resulting in pain or paresthesia at the wound site. As the virus spreads in the central nervous system, progressive encephalitis develops. Brainstem encephalitis is fatal and is characterized by hydrophobia or aerophobia, hyperactivity, and fluctuating consciousness. Phobic reflexes involve jerky inspiratory spasms as observed with this patient that may end in opisthotonos, generalized convulsions, and cardiorespiratory arrest. Bizarre behavior and a lack of focal neurological signs are common features. Priapism has been reported in some cases due to autonomic dysfunction.[1] However, rabies can present without classical symptoms of hydrophobia, as seen in this case. The disease is almost always fatal and without intensive care the patient will die within a few days. To prevent a fatal outcome, therapy must be initiated before the virus reaches the CNS and clinical signs appear. In this case, because of a lack of a clear history, the patient delayed