Neurotoxic Syndrome Developed after Taking Sertraline and Risperidone

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Neuroleptic malignant syndrome and serotonin syndrome share many common clinical features, and the term "Neurotoxic syndrome" can be used when a clear distinction cannot be made between the two. Here we present a case of 19-year-old man who experienced serotonin syndrome caused by sertraline intake, and consecutive neuroleptic malignant syndrome by risperidone. This case suggests that these two syndromes can be concomitantly induced in some patients who are susceptible to these drugs. Clinicians may have to pay close attention to this problem when prescribing drugs to patients who previously showed sensitivity to CNS-acting drugs.
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CASE REPORT

Neuroleptic malignant syndrome (NMS), one of the most serious and unexpected adverse reactions after taking neuroleptics, is characterized by a clinical triad of altered mental status, dysautonomia, and muscle rigidity.[1] The diagnosis is established on characteristic clinical features in the setting of exposure to a neuroleptic.[1] Although haloperidol has been involved in many of published cases of NMS, virtually all classes of D2 receptor antagonist can produce NMS, including prochloroperazine, metoclopramide, droperidol, promethazine, and so on.[2]

Serotonin syndrome is associated with excessive stimulation of 5-HT_{2a} and 5-HT_{1a} receptors. Clinically, it is characterized by a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.[3] It may appear after administration of drugs modulating serotonergic neurotransmission, such as monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), opiate analgesics, over-the-counter cough medicines, antibiotics, antiemetics, antimigraine agents, and herbal products.[4] The incidence of serotonin syndrome increases due to increasing use of proserotonergic agents in recent clinical practice.[3]

Since NMS and serotonin syndrome share many clinical features in common, it may be difficult to separate the two syndromes clearly, particularly when a

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subject is exposed to both classes of drugs.[5] Therefore, the term "Neurotoxic syndrome" has been used when a clear distinction cannot be made between the two conditions.[5] Here we present a case of 19-year-old man who experienced serotonin syndrome caused by sertraline, and then NMS by risperidone.

CLINICAL HISTORY

A nineteen year-old man was admitted to our hospital because of drowsiness and fever. Ten days prior to admission, he had an upper respiratory infection, and started to take medications including 50 mg/d of sertraline for depression. Two days later, he became delirious and agitated, having difficulty in swallowing, and was brought to a local hospital. He showed tachycardia, tachypnea, hyperthermia, diaphoresis and increased bowel sound. His pupil size was normal. He showed agitation, with hyperreflexia in both upper extremities, and increased muscle tone in both lower extremities. Sertraline and all other medications were withdrawn. Risperidone 1 mg/d was newly started for agitation. Three days later, he showed more severe muscle rigidity and intermittent myoclonic jerks in all limbs without improvement of initial symptoms. Subsequently, he was referred to our hospital.

He was born with no perinatal problems. He developed a febrile seizure when he was 2 years old. Subsequently, he showed mental retardation with occasional aggressive behavior. He was able to walk by himself, and communicate with others verbally. He was educated at a specialized educational institute. He was on regular medication: quetiapine (200 mg/d), benztropine (2 mg/d), propranolol (80 mg/d), and clonazepam (1.5 mg/d)] to control his aggressive behavior.

On admission, he appeared acutely ill. His systolic blood pressure was 170 mmHg, his heart rate, 170 per minute, temperature, 37.8℃ Bowel sound was not increased. He was drowsy with spontaneous eye opening and localizing response to painful stimuli. He was unable to follow verbal commands, and there was no verbal output. Pupil sizes, light reflexes, and external ocular movements were normal. There was no motor weakness. Responses to painful stimuli were symmetric. He showed marked rigidity with intermittent myoclonic jerks in all extremities. Throat examination showed tonsilar exudates with pharyngeal injection. WBC count increased to 15600 x 10^3/μl, (segmented neutrophils: 67.5%, lymphocytes: 18.7%, monocytes: 13.5%). Serum electrolytes were normal, while muscle enzyme increased (CK=7744 IU/L). Brain CT, electroencephalography and cerebrospinal fluid studies were all normal.

Ampicillin/sulbactam was started intravenously for tonsilar infection. At the first night of hospitalization, he experienced two episodes of generalized tonic clonic seizure, each lasting for 3 minutes. In suspect of serotonin syndrome by sertraline or NMS by risperidone, we discontinued all medications he was taking, and started bromocriptine (15 mg/d), L-dopa/carbidopa (300/75 mg/d), and dantrolene (50 mg/d) from the second hospital day. Right after medication changes, he showed dramatic improvement in drowsiness, myoclonic jerks and muscle rigidity. On day 3, we added clonazepam (1.5 mg/d) and tapered down datrolene, bromocriptine, and L-dopa/carbidopa slowly. On day 5, he became more alert with no myoclonic jerks. On day 7, he was discharged home with quetiapine 200 mg/d and clonazepam 1.5 mg/d for aggressive behavior.

DISCUSSION

We believe that this 19-year-old man experienced drug-induced neurotoxic syndrome: in particular, serotonin syndrome by sertraline, and NMS by risperidone.

Our patient showed mental state change, autonomic hyperactivity, and neuromuscular abnormalities, which are well known symptoms of both serotonin syndrome and NMS.[1,4]

The diagnosis of NMS is supported by hyperthermia, rigidity, elevated muscle enzyme and symptomatic improvement with bromocriptine and dantrolene.[1] On the other hand, the initial signs of agitation, diaphoresis, increased bowel sound, and myoclonus favor the diagnosis of serotonin syndrome.[4] It is likely that he had experienced serotonin syndrome induced by

sertraline, and then, NMS by risperidone. SSRI are associated not only with serotonin syndrome, but also with NMS or neurotoxic syndrome.[9] The proposed theory concerning extrapyramidal reactions occurring in SSRI involves the inhibitory effects of serotonin on dopamine activity.[9]

Differential diagnosis between NMS and serotonin syndrome is important to treat suspected patients because treatment strategies are different. NMS is considered as an idiosyncratic reaction to neuroleptic medication, whereas serotonin syndrome is due to the excessive serotonergicactivity, so dose dependent risk increase may be more prominent in serotonin syndrome than NMS.[5] Clincians' awareness of these syndromes and high suspicion are necessary for the early diagnosis and management.[1,4] Both syndromes need immediate discontinuation of offending agents, vital sign monitoring, hydration, and general supportive care.[1,4] In NMS, dantrolen and bromocriptine can be used to moderate to severe cases, but bromocriptine is known to increase CNS serotonin, so may not be used in overlap cases.[6]

The reason why this patient developed both serotonin syndrome and NMS within a short period of time remains to be explained. Several mechanisms may explain this phenomenon, such as innate susceptibility to CNS acting drugs, the co-administration of drugs that interact on several CNS neurotransmitter-receptor systems simultaneously (i.e. SSRI), and the presence of underlying medical conditions, for example, underlying mental retardation. Several drug interactions have been known to cause serotonin syndrome; phenelzine and meperidine, paroxetine and buspirone, linezolide and citalopram, etc.[4] In addition, several single agents can induce serotonin syndrome, and sertraline is one of the well-known examples.[4] In the present case, we regarded the initial episode as serotonin syndrome caused by sertraline alone and the latter as NMS by risperidone. His previous medications, such as valproate, quetiapine or clonazepam might have aggravated serotonin syndrome or NMS by drug interaction. For example, quetiapine alone may cause NMS in susceptible patients, although it is known to be more tolerable than risperidone.[10,11] However, there exists little evidence to prove the drug interaction. There have been serial cases of neurotoxic syndrome which were unable to be distinguished from NMS or serotonin syndrome.[5,7,8]

This is the first report of a neurotoxic syndrome developed serially in the same patient. We propose that there may be cross-over susceptibility between the two syndromes, and thus, clinicians should be careful when prescribing drugs to patients who have already developed one of neurotoxic syndrome.

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