Edinoff AN, Mohammad-Amin H, Odisho AS. Silent Neuroleptic Malignant Syndrome: A Case Report of Atypical Antipsychotic Induced Elevation of Creatinine Kinase and Altered Mental Status. *Health Psychology Research*. 2022;10(3). doi:10.52965/001c.37530

General

Silent Neuroleptic Malignant Syndrome: A Case Report of Atypical Antipsychotic Induced Elevation of Creatinine Kinase and Altered Mental Status

Amber N. Edinoff, MD[1] [a], Hamza Mohammad-Amin, MD[2], Amira S. Odisho, MD[2]

[1] Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital; Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Science Center Shreveport; Louisiana Addiction Treatment Center, [2] Department of Psychiatry, Louisiana State University Health Science Center Shreveport

Keywords: Schizophrenia, Neuroleptic Malignant Syndrome, Second Generation Antipsychotics, Increased Creatinine Kinase

https://doi.org/10.52965/001c.37530

Health Psychology Research

Vol. 10, Issue 3, 2022

34-year-old African American male with a diagnosis of schizophrenia was placed on aripiprazole and risperidone for psychosis and mood stabilization. Two days after medication initiation, the patient's mentation was altered and he appeared confused with an elevated creatine kinase (CK) at 7101. Medications were held and CK normalized with IV fluids. Quetiapine was initiated after medical stabilization along with lithium and paliperidone palmitate injections. After the second dose of paliperidone palmitate, the patient's mentation was altered, and repeat CK was 4272. The patient received 4 liters of IV fluid and his mental status returned to baseline.

There were two case studies noted that had marked increases in serum CK with risperidone use. The first was in an adolescent who was titrated to a dose of risperidone 3mg/ day but the only abnormality was an increase in his CK levels. The next case report was in a 40-year-old female who was on risperidone 2.5mg /day for one year. She had an intention tremor, minor muscle weakness of the lower extremities with a blood pressure of 140/100 and a pulse of 100. She manifested more clinical signs of possible Neuroleptic Malignant Syndrome (NMS). This case highlights the importance of laboratory investigations when there is a high suspicion of possible NMS. It also highlights that some cases of NMS may only present as altered mental status and increased CK in which quick treatment may lead to the prevention of full-blown clinical manifestations of NMS which could be life-threatening.

INTRODUCTION

Atypical Antipsychotics are known for their post-synaptic blockade of the dopamine D2 receptors along with 5-HT2a antagonism with the exception of aripiprazole and brexpiprazole which are partial D2 agonists. Aripiprazole also has serotonin 5-HT1A receptor partial agonism. The evidence that supports these receptors in the activity of antipsychotics in a study performed by Kapur et al in 2000. This study showed that there is a consistent requirement of 65 percent D2 receptor blocking occupancy for antipsychotic efficacy in functional imaging studies.[1] A higher percentage of D2 blocking is associated with a higher side effect profile and the possibility of more severe adverse events. One of these adverse events is of special concern especially since it is dangerous. This is Neuroleptic Malignant Syndrome (NMS). NMS is characterized by rigidity, altered mental status, fever, and dysautonomia.[2,3] One laboratory marker that can be seen is increased serum creatine kinase (CK) levels which is a marker of muscle breakdown. This increase in CK can also be a sign of Rhabdomyolysis. NMS happens in about 0.02 to 3 percent of those who are taking antipsychotics.[4] NMS most commonly happens with the use of first-generation antipsychotics (i.e. Haloperidol,

a **Corresponding author**:
Dr. Amber Edinoff, MD
Massachusetts General Hospital
Department of Psychiatry
55 Fruit St
Boston, MA, 02114
Phone: (617) 726-2000
aedinoff@mgh.harvard.edu

Fluphenazine) but it has also been associated with second-generation antipsychotics.[5] Hyperthermia or hypothermia is common in around forty percent in patients with NMS, along with tremor in 42 to 90 percent.[2] Autonomic instability can also occur in the form of tachycardia (up to 88 percent), labile or high blood pressure in 61 to 77 percent, and tachypnea in 73 percent.[6,7] In other words, there are many accompanying signs that will alert the clinician to the existence of possible NMS caused by antipsychotic use aside from laboratory studies.

What if there are not any of the usual signs that would lead a clinician to think about NMS? There could be some cases that are not as obvious but still need to have a high degree of suspicion as it could still be dangerous to the patient. This is a case about a patient where the only suspicion that something was wrong was that the patient appeared to have an altered mental status which presented as a regression in the treatment of his psychosis and disorientation. This is a case of a 34-year-old male who had increased CK level after restarting atypical antipsychotics which presented as a difference in his baseline mental status.

CASE

34-year-old African American male with a past psychiatric history significant for Schizophrenia and Mild Intellectual Disability and no significant past medical history presented to the emergency department for suicidal ideation, homicidal ideation towards to his mother, and auditory hallucinations. He answered in single word sentences when asked what brought him to the hospital which sometimes included just the word "suicide." He was admitted to the inpatient unit for further stabilization. He was started on aripiprazole 20mg a day and risperidone 3mg twice daily as they were his home medications. Two days after admission, the patient appeared confused and more altered than on admission. Laboratory testing was obtained and serum CK level was found to be elevated at 7101 U/L. The patient was hydrated with IV fluids and both aripiprazole and risperidone were both held at this time. His mental status shortly returned to his baseline that was present when he was admitted to the unit. The treatment focus was then shifted to stabilizing the patient with the use of quetiapine. Later in the admission, oral paliperidone was started with the idea of transitioning the patient to a long acting injectable antipsychotic to increase compliance and to further address refractory psychosis which was not fully controlled on quetiapine. Lithium carbonate 300mg twice a day was also added for mood stabilization and to address continued suicidal ideation shortly after paliperidone was started. The first injection of paliperidone palmitate 234mg was given without incident and the patient's mental status remained the same. After the second injection of paliperidone palmitate 156mg, the patient's mental status started to become altered again which presented as a regression in his psychotic symptoms along with confusion. He started to exhibit more severe thought blocking and was responding to internal stimuli along with not being oriented to time or place. It should be noted that the patient received intramuscular injections of haloperidol 10mg after this mental status change took place as he was unable to be redirected by the staff and each injection occurred on two separate occasions. The regression was to the point where the patient could not hold a conversation with his treatment team in sentences that were more than one or two words in length which was similar to his original presentation as well as having delays in his answers. Before this happened, he was speaking in complete sentences and was able to immediately answer questions posed by the team. More laboratory studies including a complete blood count, comprehensive metabolic panel, CK level, and ammonia level were obtained due to the patient's change in mental status. The CK level was found to be increased again at 4272 U/L and all other labs were noted to be non-concerning. After two liters of IV fluid, the patient's creatine kinase trended down to 3044 U/L and after two more liters the creatine kinase trended to 1242 U/L. After these four liters of fluid, the patient's mental status greatly improved to where he was communicating with the team in full sentences again, response time was improved, and orientation was restored. On discharge, the patient's final CK level was noted to be 321 U/L and the patient's medication at that time was quetiapine 800mg with the paliperidone palmitate injection still on board as well as lithium 600mg twice daily. The discharge plan was to continue the patient's stabilization on an outpatient basis with quetiapine due to this reaction.

DISCUSSION

There have been a few case reports of increased levels of serum CK that were associated with either typical or atypical antipsychotic use. One of the case reports was a patient who was on clozapine and ziprasidone was added for refractory psychotic symptoms.[8] The patient had received an epidural for a herniated disc 10 months after starting ziprasidone. On routine lab monitoring due to clozapine use, the patient's white blood cell count and absolute neutrophil count were noted to be elevated. The patient's vital signs were stable, EKG was unremarkable, and the only other laboratory abnormality found was an increased CK level. This CK level was noted to be elevated at 26,152 U/L. The author noted no changes in cognition which was the opposite of what was noted in the patient in the case discussed in this report. The patient was hospitalized, both antipsychotics were held, and the patient was treated with IV fluids. The CK decreased to below 500 U/L and medications were resumed with ziprasidone started at a lower dose. The CK stayed slightly above the normal limits even with this lower dose of ziprasidone. This case highlighted that a high index of suspicion must be maintained with any clinical signs suggestive of NMS.

Another study looked at the cases of increased CK in association with the use of second-generation antipsychotics compared with the use of first-generation antipsychotics. They found that 17% of the patients receiving clozapine or olanzapine, the second-generation agents used in this

study, had CK measurements above the upper normal limit whereas none of the patients receiving first-generation agents such as haloperidol had this increase. Interestingly, none of the patients' reported muscular symptoms such as pain or rigidity.[8] A study looked at 11 cases in which increased CK levels were seen with the use of clozapine, olanzapine, loxapine, melperone, risperidone, and haloperidol.[9] In all the cases highlighted, there was a notable increase in CK, however, there was no evidence of muscle trauma or hyperactivity. Only one of the cases in this study had at least one of the major features of NMS which were muscular rigidity, autonomic instability, or fever. There have been several case reports of increased CK activity in clozapine-treated patients that have been ascribed to NMS without muscular rigidity.[10,11] The patient discussed in the case presented also never complained of muscle pain or rigidity and all of his vital signs remained stable.

There were two case studies that noted marked increases of serum CK with risperidone use which is of interest since the patient in this case study was on risperidone first with an elevated CK level, then had another elevation of his CK level with paliperidone palmitate, an injectable metabolite of risperidone, and that both were associated with an altered mental status. The first was in an adolescent with a diagnosis of catatonic psychosis.[12] This patient was treated with risperidone and this was titrated to a dose 3.5 mg per day. After three weeks of treatment and discontinuation of his lorazepam which was used for catatonia, his CK started to climb at 129 U/L. The patient complained of restlessness and facial myalgia which was thought to be associated with benzodiazepine withdrawal and diazepam at 15mg a day was started. The addition of diazepam had no effect on these symptoms. A week later, the CK was noted to have peaked at 9743 during which time the patient had no extrapyramidal symptoms, changes in cognition, or changes in psychomotor activity. CK levels returned to normal have discontinuation of risperidone. The next case report was on a 40-year-old female who was on risperidone 2.5mg daily for one year.[13] The other medications the patient was on during this time included clomipramine 100mg, lithium 400mg, lorazepam 2mg, and nozinan 25mg. She was noted to have intention tremors, minor muscle weakness of the lower extremities and tender calf muscles, a blood pressure of 140/100, and a pulse of 100. She was found to have a high creatinine and elevated liver enzymes. Her CK rose to 35,1100 U/L and she developed anuria, liver failure, and was placed on intermittent hemodialysis. The authors contributed the use of risperidone as the possible cause for the increase in her CK levels though it was unclear if the medication was stopped in this report as it was not specifically mentioned. She eventually recovered with aggressive treatments and ICU admission. They did mention that NMS was a part of their differential but stated that they did not feel that she met the full criteria for the diagnosis.

CONCLUSION

In the case of this patient mentioned in this report, he showed no other signs of NMS other than being altered in terms of his mental status. He seemingly had been regressing and becoming more psychotic after his second dose of Paliperidone Palmitate though that was the only sign that pointed to a potential side effect that should be investigated. It should be noted that during this regression, he did receive two intramuscular injections of Haloperidol due to his inability to be redirected by nursing staff. It should also be noted that these injections are given to many patients who do not develop an increased CK or develop an altered mental status through intramuscular injections, in general, could cause muscle damage that could cause an increase in serum CK. He was already displaying this altered mental status when these injections were given. His vital signs were stable, he never complained of muscle pain, and he never displayed any muscle rigidity. Perhaps, this could be NMS even without all the clinical signs that are usually seen in this syndrome. This change in mental status and subsequent increased CK levels on laboratory investigations were found within days of the initiation of the possibly offending medication. In every other case discussed in this section the increase was noted to be happened between weeks and a year after the initiation of the associated antipsychotic. It could be argued that this could have been at the very least the beginning of NMS and could have progressed to the manifestation of other clinical symptoms that could have been seen in his vital signs or physical examination. This means that the clinician must have a high degree of suspicion whenever there is a change in the patient that could warrant investigation and treatment of this potentially dangerous condition.

ACKNOWLEDGEMENTS

The authors would like to thank the patient for his permission to present his case for teaching purposes in a publication.

REFERENCES

1. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. *American Journal of Psychiatry*. 2000;157(4):514-520. doi:10.1176/appi.ajp.157.4.514

2. Caroff SN, Mann SC. Neuroleptic malignant syndrome. *Medical Clinics of North America*. 1993;77(1):185-202. doi:10.1016/s0025-7125(16)30278-4

3. Velamoor R. Neuroleptic malignant syndrome: A neuro-psychiatric emergency: Recognition, prevention, and management. *Asian Journal of Psychiatry*. 2017;29:106-109. doi:10.1016/j.ajp.2017.05.004

4. Velamoor VR. Neuroleptic malignant syndrome. *Drug Safety*. 1998;19(1):73-82. doi:10.2165/00002018-199819010-00006

5. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *American Journal of Psychiatry*. 2007;164(6):870-876. doi:10.1176/ajp.2007.164.6.870

6. Levenson JL. Neuroleptic malignant syndrome. *American Journal of Psychiatry*. 1985;142(10):1137-1145. doi:10.1176/ajp.142.10.1137

7. Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. *American Journal of Psychiatry*. 1989;146(6):717-725. doi:10.1176/ajp.146.6.717

8. Agarkar S. Elevated creatine kinase levels with second-generation antipsychotics. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2011;23(3):E49-E50. doi:10.1176/jnp.23.3.jnpe49

9. Meltzer HY, Cola PA, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. *Neuropsychopharmacology*. 1996;15(4):395-405. doi:10.1016/0893-133x(95)00276-j

10. Nopoulos P, Flaum M, Miller DD. Atypical neuroleptic malignant syndrome (NMS) with an atypical neuroleptic: Clozapine-induced NMS without rigidity. *Annals of Clinical Psychiatry*. 1990;2(4):251-253. doi:10.3109/10401239009147953

11. Goates MG, Escobar JI. An apparent neuroleptic malignant syndrome without extrapyramidal symptoms upon initiation of clozapine therapy: Report of a case and results of a clozapine rechallenge. *Journal of Clinical Psychopharmacology*. 1992;12(2):139-140. doi:10.1097/00004714-199204000-00016

12. Holtmann M, Meyer AE, Pitzer M, Schmidt MH. Risperidone-induced Marked Elevation of Serum Creatine Kinase in Adolescence: A Case Report. *Pharmacopsychiatry*. 2003;36(6):317-318. doi:10.1055/s-2003-45121

13. Castelijns MH, Keeris LM, van der Hoeven JH. Risperidone-induced severe rhabdomyolysis: a case report. *Clinical Case Reports and Reviews*. 2016;2(6). doi:10.15761/ccrr.1000241