

Asymptomatic CK Increase in Patient with Neuroleptic Sensitivity after the Development of Neuroleptic Malignant Syndrome

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Abstract: *Neuroleptic malignant syndrome NMS is a life-threatening condition associated with the use of antipsychotic medications, primarily resulting from rapid dosage changes or abrupt discontinuation. This article explores the risk factors, clinical presentation, diagnosis, and treatment of NMS, with a focus on a unique case involving a 41-year-old male with paranoid schizophrenia. The patient experienced NMS after discontinuing Clozapine, with an unexplained recurrence 14 days later. Genetic factors and pharmacogenomics are discussed as potential contributors to NMS susceptibility. The importance of early recognition and monitoring in atypical NMS presentations is emphasized, given the high mortality rate associated with this condition. This case highlights the need for further research and guidelines in patients prone to medication side effects and those at risk of NMS, aiming for more individualized and safer prescribing practices.*

Keywords: Neuroleptic malignant syndrome, antipsychotic medications, schizophrenia, genetic factors, pharmacogenomics

1. Background

Neuroleptic malignant syndrome (NMS) is a life-threatening condition that can be caused using antipsychotic medications; however, it most commonly occurs due to rapid increases in dosage or abrupt cessation of these medications, especially if the medication is highly potent or in the form of depot injection. (1)

The risk of NMS is increased in the case of a rapid decrease in dopamine availability at post-synaptic receptors but will also be affected if antagonism at the dopamine receptor is persistent. (2)

In addition to typical and atypical neuroleptics, numerous offending agents have been suggested as potential incriminating agents including antiemetic medications, Lithium, and tricyclic antidepressants. It has been reported that NMS can occur with the long-term use of low dosage of antipsychotics such as Risperidone when combined with anticholinergic drugs. (1, 3, 4)

The incidence of NMS is reported to be between 0.01% and 3.2% of patients who take neuroleptics. It occurs most frequently in young males. (5)

The symptoms of NMS can develop over one to three days. DSM-V outlines all the major criteria including dopamine blocking agent exposure, severe muscle rigidity, and fever along with at least two out of ten further criteria which need to be present for diagnosis. Such criteria include diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leucocytosis, and elevated creatinine

phosphokinase. (1) The clinical diagnosis of NMS is challenging due to the variety of presentations possible. (6) Diagnosis is supported by blood testing to include creatinine phosphokinase level, full blood count, renal function tests, liver function tests and blood gas tests to screen for metabolic acidosis. Leucocytosis is also common as well as abnormalities in transaminase levels. (1) In order to establish the diagnosis of NMS, it is important to distinguish NMS from other conditions which present with similar features. In some conditions, the offending agent offers a variation in presentation which aids its differentiation from the NMS.

NMS can sometimes be confused with serotonin syndrome related to SSRI use. However, serotonin syndrome presents with fever, muscle rigidity with GIT disturbances as well as hyperreflexia and myoclonus being more pronounced. It is important to consider that malignant catatonia also has similar features, however, this has a rapid response to initiation of benzodiazepines and full recovery occurs in 80% of such cases. Medical conditions that can show similar features to NMS include meningitis, encephalitis, delirium, acute intoxications and withdrawal from alcohol, benzodiazepines, and substances like cocaine, MDMA, amphetamines, and phencyclidine as well as non-convulsive status epilepticus and metabolic emergencies like thyrotoxicosis and pheochromocytoma. (1)

The pathophysiology of NMS is not entirely clear, however, there are reports of how D2 receptor blockade or abrupt withdrawal of D2 receptor stimulation appears to have an influence on the development of muscle rigidity, hyperthermia, and mental status. It has been suggested that some symptoms can be explained by sympathetic disruption. Simon L.V et al, 2023 have reported that calcium-mediated

disruption of the musculoskeletal system is also seen in malignant hyperthermia. (1)

Genetic factors are suggested as predisposing factors contributing to the development of NMS and may provide a solution for the treatment of patients with a family history of NMS and with a personal and family history of neuroleptic sensitivity. Numerous reports have highlighted a statistical correlation between polymorphisms and NMS however the exact pathway remains unclear. (1, 2, 7)

Treatment should include hydration and supportive therapy, dopaminergic agonists such as Bromocriptine can be used orally or via a nasogastric tube. Muscle relaxants in intravenous or oral form can also be considered. ECT is proven to be efficient in refractory cases of NMS when necessary. (8) If treatment has been initiated in a timely manner, full recovery is expected between two to fourteen days. It is generally recommended to wait at least two weeks before recommencing antipsychotic medication to monitor for symptoms of NMS recurrence.

2. Case Presentation

We wish to present the case of a 41-year-old gentleman, with an extensive forensic history along with paranoid schizophrenia, who presented with an explainable occurrence of neuroleptic malignant syndrome after abrupt cessation of Clozapine due to deterioration of his mental state in the context of poor compliance with his medication regime, and the unexplainable re-occurrence of NMS 14 days after initial presentation. The patient has a history of alcohol misuse, erratic medication compliance and multiple admissions to the psychiatric unit. Apart from well-managed hypertension, this patient had no other significant medical history of note. The patient was admitted to the acute mental health unit in March 2023 after he self-presented to the emergency department with anxiety, low energy, anhedonia, and generalized stiffness. His mental state had deteriorated following non-compliance with long-term prescribed Clozapine for an unknown period. At that time, he was prescribed 150 mg of Clozapine in the morning, and 250 mg in the evening-time.

During the first hours of admission, he presented with pyrexia and body temperature of 38.1°C, muscular rigidity, bradykinesia, tremor, and hyperreflexia, along with fluctuating level of consciousness that varied between lethargy and confusion. His other vital signs were within normal range limits. After initial physical examination, laboratory work-up and ECG, he was transferred to the medical ward with elevated Creatine Kinase (CK) levels (999) and leucocytosis (13.4) under suspicion that he might suffer from neuroleptic malignant syndrome. After initial admission to the intensive care unit where he remained for two days for diagnostics and observation, he was transferred to the medical ward for another three days and discharged back to the mental health unit with advice to keep him off the medications with regular laboratory review. Two weeks after first episode of NMS, he developed asymptomatic CK elevation which was detected with routine laboratory tests in the post NMS recovery follow-up investigations. The patient was transferred back to the medical ward after his CK levels

doubled in a 24-hour period without any symptoms to support CK elevation and excluding other organic or non-organic CK elevation causative factors, including the psychotropic medications use, after thorough medical diagnostic work-up. The patient also had a history of numerous side-effects of psychotropic medication ranging from dopaminergic and serotonergic side-effects to even onset of catatonia in the past that was psychotropic medication related as per findings in patient's documentation file. In the past he has been trialled on Olanzapine which was discontinued after he developed hypotension and tachycardia. He had another trial of Olanzapine soon after and developed significant QTc prolongation in ECG findings. While he was treated with Haloperidol in the past, he complained of severe tiredness and there was marked weight gain consequently because of tiredness related to a lack of physical activity. He had similar side-effects when treated with Risperidone, along with akathisia, which he had developed on treatment with Haloperidol as well. According to the patient documentation on file, while the patient reported no side-effects or physical complaints when treated with Amisulpride, but this medication led to no improvement in his mental state which subsequently led to re-admission to the acute mental health unit. The patient, also, did not experience any improvement when treated with Aripiprazole. Due to the above-mentioned unsuccessful medication trials, in the context of treatment-resistant and challenging paranoid schizophrenia, the mental health team decided to introduce Clozapine for this patient.

3. Investigations

On admission to the intensive care unit, as mentioned before, the patient was noted to have increased body temperature, muscular rigidity, bradykinesia, tremors, and hyperreflexia, along with fluctuating level of consciousness. His CK levels had doubled in first 24 hours of admission to ICU, from 999 to 1831. His WBC (leucocytes) were elevated, 13.4. Apart from elevated CK and leucocytosis, other blood laboratory findings were within the normal range, including troponins, CRP, liver and kidney functions. Neuroimaging, the CT brain was done as part of physical investigation and revealed no abnormalities. The chest XR was clear and the analysis of MSU showed no signs of infection or any other abnormalities. Lumbar puncture for cerebrospinal fluid analysis was not performed as there was no observed rise in CRP and no clinical signs of meningitis and encephalitis present.

The patient was transferred back to the mental health unit, after four days of medical admission, when his CK levels dropped to 800, with the recommendation to continue with daily monitoring of FBC, CK, and U&Es. Medications prescribed on discharge from the medical ward included Esomeprazole, Cholecalciferol, Propranolol, Diazepam, Procyclidine, and Lactulose.

14 days after the patient was discharged from the medical ward post-neuroleptic malignant syndrome but still under daily follow-up of laboratory tests for FBC, CK, and U&Es, he developed an asymptomatic increase in CK level, which doubled in 24 hours (390), and tripled in 72 hours (1188). He had a brief episode of pyrexia which normalized soon

after transfer to the medical ward and responded well to treatment with Paracetamol.

Acute onset CK re-elevation led to readmission to the medical ward with a working diagnosis of CK increase of unknown cause. After thorough physical and laboratory investigations, there were no findings indicating any organic or non-organic cause of sudden CK increase.

The patient was transferred back to the acute mental health unit when his CK dropped below 600 with the same recommendation as after the earlier mentioned discharge.

4. Treatment

The patient was treated with intravenous fluids on both occasions after being admitted to the CCU and the medical ward. On the second admission, Paracetamol was introduced to treat a high temperature. The patient reported ongoing sleep disturbance and commenced a short course of Zopiclone. Promethazine was charted as needed, however, according to the medical records was never given by nursing staff and was ultimately discontinued.

5. Follow up

From the middle of April 2023, Clozapine has been restored following the return of CK and FBC levels back to the normal range. Observation of the patient's vitals was performed every four hours and the patient appeared to be stable and asymptomatic. An overall improvement in his mental state was also noted. He appeared to be more reactive with better fluency of speech and cohesive thinking. There has not been any deterioration in his physical health since his recovery.

6. Discussion

The relationship between catatonia and NMS has been studied by several authors. Clinical onset, signs and symptoms may be very similar. Views range between authors, from the two being considered as two distinct entities, to NMS possibly being an antipsychotic aggravated form of catatonia (9).

Although there is a lack of information about the patient's family history due to reported dysfunctional familial inter-relations, we cannot exclude a possible genetic component in variability influenced drug response and tolerability. Antipsychotics are used in the treatment mainly of schizophrenia and related psychotic disorders but also show efficacy in the treatment of other psychiatric disorders. There is a significant inter-individual variation in the therapeutic efficacy and tolerability of antipsychotics, and this represents a significant challenge for physicians and their patients in planning and deciding about treatment options. Evidence from twin studies implicates a significant genetic component underlying individual differences in susceptibility to AAEs (10). Pharmacogenomics, a field of study for this inter-individual variability influenced by genomic factors (11), is undergoing significant development, and will ultimately help to change the face of medicine when

it comes to pharmacotherapy, clinical development, and an individual, patient-centred approach.

Once neuroleptics are stopped, NMS is usually self-limited and lasts approximately 7 to 10 days; however, in some cases, residual symptoms may persist (12), which was thankfully not the case for this patient. Other possible organic and non-organic risk factors for the development of re-occurrence of the neuroleptic malignant syndrome, such as the presence of agitation; dehydration or physical restraints; concomitant administration of lithium; abrupt withdrawal of dopamine agonists, anticholinergics, or benzodiazepines (BDZ); the presence of organic brain syndromes or extrapyramidal symptoms; and iron deficiency have been extensively considered and excluded (12).

Some publications have described cases of unknown causation and a unique clinical course of neuroleptic malignant syndrome (13), which is also a possibility in this case because of the unknown cause of relapse of NMS within the 14 days of resolution of the initial presentation, and especially concerning an inpatient who was off the potential causative neuroleptic agents with, apart from elevated CK levels, an asymptomatic presentation. A relevant point in this case is the necessity for the medical and health care staff to have a high level of expertise in the early recognition of neuroleptic malignant syndrome, as mortality for NMS remains high according to available statistical data (20%) (14). In atypical presentations such as in this case, asymptomatic relapse of neuroleptic malignant syndrome with elevated CK, and with no detectable underlying causative factor, there is a potential risk of undetected progression of neuroleptic malignant syndrome which could result in fatal complications.

It has been established that CK levels depend on sex, race, and levels of physical activity. In some cases, an increase in CK is of idiopathic cause. D'Adda et al. 2006 followed 55 patients who had increased CK levels for 7 years. 80% did not develop any condition, while 10% were diagnosed with malignancy and a neuromuscular disorder. Many cases continued to have asymptomatic increases in CK over time. (15) While considering variations in the presentation of NMS versus asymptomatic increase in CK, it is important to keep in mind that a patient can develop malignancy or neuromuscular disorder as suggested by the literature.

Further case reports, research, and guidelines are recommended for any potential future presentations, especially in patients prone to medication side-effects, or previously, or de-novo identified risk factors. Pharmacogenomics might be key, therefore, to reduce this risk regarding more individualised future prescribing.

7. Conclusion

Neuroleptic malignant syndrome is a complex and life-threatening condition associated with antipsychotic medications. This case study underscores the significance of early recognition and monitoring in atypical presentations, as well as the potential role of genetic factors and pharmacogenomics in understanding susceptibility to NMS. As we move towards more individualized medicine, further

research and guidelines are crucial to improve patient safety and reduce adverse reactions in individuals prone to medication side effects. This case also highlights the importance of patient cooperation and sharing of experiences to enhance our understanding of rare and challenging clinical scenarios.

8. Data Availability

Data used to support the findings of this study are included in the article.

9. Additional Points

Adapted from the patient: The patient was cooperative and keen to share the relevant information on how he felt after being admitted to the medical ward on two occasions. He is aware of his sensitivity to medications and stated that he is happy to share his story and if possible, to prevent it from happening to someone else.

Ethical Approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for the publication of this case report was not required by their local ethics committee.

Disclosure

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Conflicts of Interest

The authors, DrJelena Vojnic Barisic, DrMaura Grummell, DrIvona Kusen, Dr Martina Quinlan do not have any conflicts of interest to report.

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