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Exceptionally high creatine kinase levels in risperidone-induced neuroleptic malignant syndrome: A case report

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Abstract

Neuroleptic malignant syndrome is a rare, fatal antipsychotic-induced idiosyncratic reaction characterised by hyperthermia, altered consciousness, autonomic instability and rigidity with elevated creatine kinase levels and leukocytosis. Neuroleptic malignant syndrome and antipsychotics are significant causes for elevated creatine kinase among the extensive list of differential diagnoses. Risperidone is an atypical antipsychotic drug with anti-serotonergic and anti-dopaminergic properties which has a wide range of side effects, including neuroleptic malignant syndrome. Though the rise in creatine kinase in neuroleptic malignant syndrome is commonly around 2000 to 15,000 IU/L due to myonecrosis, ischaemia and heat production, normal creatine kinase levels in neuroleptic malignant syndrome were also reported. Up to now, only two cases have been reported with creatine kinase levels of more than 50,000 IU/L in neuroleptic malignant syndrome, but neither of them was risperidone-induced. We report the first case of an exceptional rise in creatine kinase levels more than 250-fold in a 16-year-old girl following low-dose risperidone-induced neuroleptic malignant syndrome.

Keywords

Neuroleptic malignant syndrome, creatine kinase, risperidone, rhabdomyolysis

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Introduction

Neuroleptic malignant syndrome (NMS) is an uncommon, fatal idiosyncratic reaction characterised by hyperthermia, altered consciousness, autonomic instability, rigidity, elevated creatine kinase (CK) and leukocytosis.[1,2] It occurs in 0.04% of the population who receive antipsychotic drugs, probably due to their anti-dopaminergic action.[3]

CK is a dimeric protein that is mainly found in the skeletal muscle, heart and brain. Differential diagnoses for elevated CK are broad, including NMS and antipsychotic intake. Risperidone is an atypical antipsychotic drug with more anti-serotonergic rather than anti-dopaminergic activity and fewer extrapyramidal side effects. Because of this feature, it is less likely to induce NMS.[4]

Although elevated CK in NMS has been reported in more than 90% of cases, there can be instances where CK levels could be within the normal reference range.[5] To the best of our knowledge, here we report the first case of risperidone-induced NMS with elevated CK levels above 50,000 U/L, which returned to normal following successful treatment.

Case presentation

The patient was a 16-year-old girl treated with risperidone (1 mg/day for 5 days) for depressive features that alternated with elevated mood. The patient was admitted to the hospital with a history of behavioural changes and sleeplessness for a week. She was otherwise healthy, had no history of muscle injury and did not take any other medicines apart from risperidone.

On admission, the patient was febrile (102.8°F; 39.3°C), had upper limb rigidity and a Glasgow Coma Scale score of 12 (normal score is 15) derived totalling four of four in eye response, three of five in verbal response and five of six in motor response.[6] With these exceptions, the systems review

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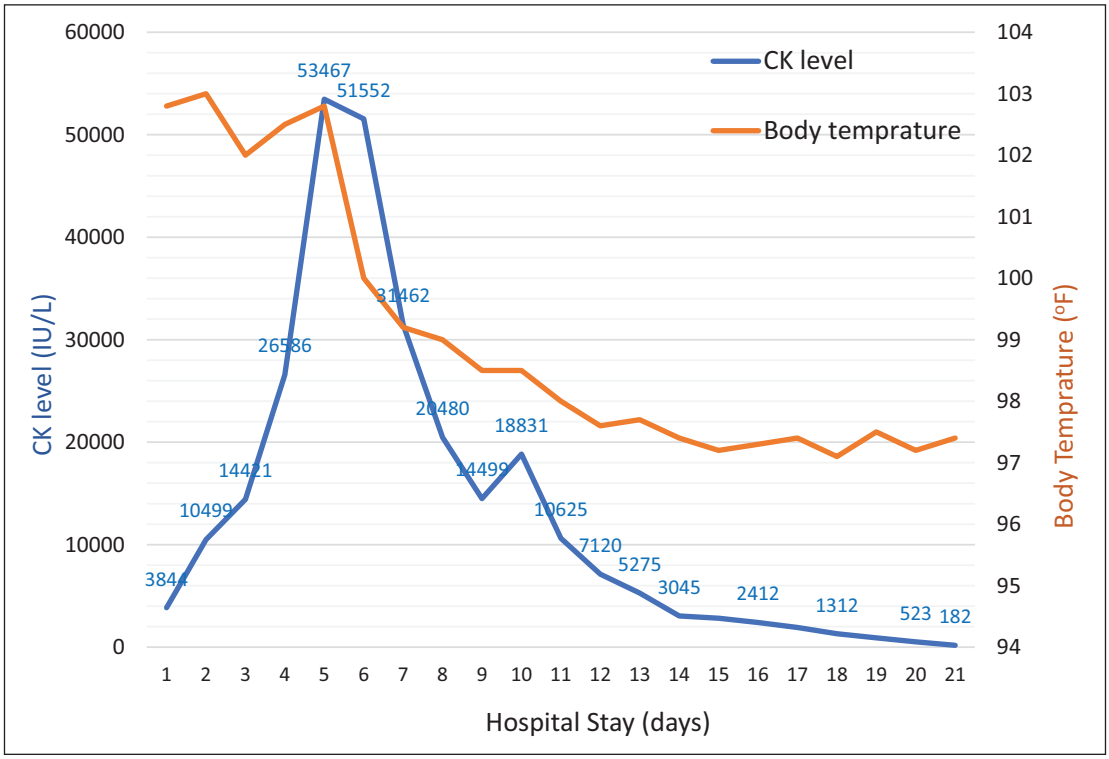

Figure 1. CK levels along with body temperature of our patient during hospital stay.
CK: creatine kinase.

and physical examination were normal, including the patient's pulse rate and blood pressure.

On the day of admission, the patient had a CK of 3844 IU/L (reference range 25–174 IU), which increased to 53,467 IU/L on day 5 and then gradually decreased to182 IU/L on day 21. Figure 1 outlines the trend of our patient's CK level and body temperature during the hospital stay. The patient's serum creatine and blood urea concentrations throughout the hospital stay did not rise beyond the reference values.

Other investigations revealed metabolic alkalosis (pH 7.53 (reference range 7.35–7.45), pCO_2 46 mm Hg (35–45 mm Hg), bicarbonate 38.4 mmol/L (22–28 mmol/L)); elevated transaminases (aspartate transaminase 203 U/L (5–34 U/L) and alanine transaminase 102 U/L (10–40 U/L)); hyperkalemia 5.5 mmol/L (3.5–5.1 mmol/L); hypocalcaemia 7.3 mmol/L (8.6–10.2 mmol/L) and neutrophilic leukocytosis (white blood corpuscles count of 13,300/µL (4000–10,000/µL) with 75.4% neutrophils). Computed tomography of the brain showed cerebral oedema. Electroencephalography revealed a low voltage record with a poorly defined background. The rest of the laboratory findings, including serum sodium, thyroid-stimulating hormone, C-reactive protein (CRP) and iron studies (serum ferritin, iron, total-iron binding capacity, unsaturated iron-binding capacity and iron saturation), urine full report and spinal fluid analysis, were all within normal limits. Body fluid cultures were devoid of any growth.

The patient was diagnosed with risperidone-induced NMS. Apart from discontinuing risperidone, she was managed with oral lorazepam, intravenous paracetamol, tepid sponging and adequate hydration. The patient's electrolytes imbalance was managed successfully.

Discussion

Rhabdomyolysis, polymyositis, Duchenne muscular dystrophy and myocardial infarction are causes of elevated CK levels beyond the 10-fold upper normal limit.[7] NMS is a significant cause for rhabdomyolysis apart from traumatic and exertional causes.

All three major Levenson's criteria, namely hyperpyrexia, rigidity and elevated CK, have been fulfilled in this case to diagnose NMS.[1] Elevated CK is a cardinal feature of NMS but not pathognomonic, and cases of NMS without elevation of CK are also reported.[2,5] In these circumstances, NMS can be diagnosed from the clinical background using other diagnostic criteria.[5] CK elevation in NMS occurs mainly due to intense muscle contractions causing myonecrosis, ischaemia and heat production.[2]

NMS can occur even with the lowest possible therapeutic doses of risperidone (0.5 mg/day), especially when given with cholinergic drugs.[8] In this case, NMS occurred with a short course of low dose risperidone, that is, 1 mg/day for 5 days.

Table 1. Risperidone-induced NMS cases with CK values.

Authors	Maximum CK level (IU/L)
Bajjoka et al.[4]	6974
Espiridion et al.[17]	4842
Vázquez and Beltrán[18]	4026
Chen and Chen[19]	3196
Mané et al.[20]	1920
Park and Il Park[21]	1181

Several cases of high CK activity are reported with various antipsychotic drugs, both with the absence and presence of NMS.[1,9–13] Massive asymptomatic CK elevation (MACKE) following antipsychotics is also possible even in the absence of NMS, and its significance is unknown.[14] Several studies concluded that the median serum CK level was significantly higher in patients receiving atypical antipsychotics like clozapine or olanzapine than conventional agents.[11,14]

The rise in CK in NMS is typically around 2000–15,000 IU/L.[1] Levenson[1] has reported two NMS cases with CK levels exceeding 50,000 IU/L and a case with 100,000 IU/L following chlorpromazine- and benztropine mesylate-induced rhabdomyolysis without NMS. Look et al.[15] reported a case with a CK of 73,780 IU/L due to risperidone-induced rhabdomyolysis, but without NMS. Meltzer et al.[9] reported 11 cases of markedly elevated CK activity with various antipsychotic drugs in the absence of NMS, where a young female had 177,000 IU/L of CK following loxapine treatment, and the peak level of CK following risperidone treatment was 9571 IU/L.

The first case of NMS was reported in 1960 by Delay et al.[16] Since then, no cases have been reported with a CK value of more than 50,000 IU/L due to risperidone-induced NMS. Table 1 outlines recently published cases of risperidone-induced NMS with CK values more than 1000 IU/L but not even exceeding 10,000 IU/L.

In accordance with the literature, this case also had leukocytosis within the range of 10,000–40,000/mm^3; mild elevation in transaminases; hypocalcaemia; hyperkalemia; cerebral oedema and an electroencephalographic pattern of diffuse slowing without focal abnormalities.[1,4,10] The latter two findings were reported in the literature due to severe metabolic derangements, and they help differentiate NMS from structural brain damage and non-convulsive status epilepticus, respectively.[10] No growth in cultures and normal CRP excluded infective causes. Late complications of rhabdomyolysis such as acute renal failure, disseminated intravascular coagulation or compartment syndrome were not seen in this case.

Cerebral oedema is a significant condition with various causes, but it was reported to occur only in two cases apart from our case of NMS due to severe metabolic derangements.[22] Blasi et al. hypothesised that cerebral oedema results from hyponatraemia which was not evident in this case. We believe that a more detailed assessment of cerebral oedema in patients with NMS is indicated.

Discontinuation of the causative drug is the most important treatment in NMS. This will normalise the CK levels in NMS and primary antipsychotic-induced benign CK elevation.[12] Supportive treatment includes maintenance of adequate hydration, nutrition, and cardiorespiratory stability. Fever can be treated with cooling and acetaminophen. Still, high temperature in NMS due to internal head load may not respond to acetaminophen and usage of antipyretics is not well established in the literature.[13] Not many clinical trials are available regarding the efficacy of specific medical treatment in NMS. Still, dantrolene, bromocriptine and benzodiazepines (lorazepam or diazepam) can be used in combination with supportive treatment.[2,10] Electroconvulsive therapy with succinylcholine for adequate muscle relaxation is effective in severe NMS.[2]

Emergency department encounters with a history of antipsychotic intake and elevated CK levels should be evaluated, considering NMS as one of the important differential diagnoses apart from brain structural and infective causes.

High CK values are commonly reported in antipsychotics-induced NMS and MACKE. However, exceptionally high CK levels more than 250-fold rise can also occur after short-term treatment with a low dose of risperidone, despite this drug's less anti-dopaminergic action. Using a holistic clinical evaluation aided by different diagnostic criteria to diagnose NMS is important.

Very high CK values can lead to early and late complications of rhabdomyolysis. Management of risperidone-induced NMS encompasses omitting the causative drug, supportive medical treatment and preventive treatment for complications of rhabdomyolysis.

We strongly emphasise the possibility of NMS with a low dose of risperidone monotherapy with exceedingly high levels of CK, which can progress to life-threatening complications to improve vigilance on this rare but important topic.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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