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# Neuroleptic Malignant Syndrome and Extremely High Creatine Kinase Level; 2 Episodes in One Patient: A Case-Report

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**Abstract** **Case Report**

***Background*:** The neuroleptic malignant syndrome (*NMS*) is an idiosyncratic abnormality due to the use of dopamine antagonists. The most incriminated are antipsychotics, these drugs can be classified according to the incidence of this iatrogenic event. Amisulpride and Risperidone are not on the top of the list; they are not reported sufficiently in the literature because of the rarity of the event. ***Case presentation*:** We report, through this case-report, a patient who had two successive episodes of NMSs, this is a rare event in psychiatric practice that let us take in consideration the genetic hypothesis of individual vulnerability. In addition, the plasmatic creatine kinase being at 50,000 iu/l is not very common and put our patient in a life-threatening situation. ***Conclusion*:** Although being rare, the neuroleptic malignant syndrome can occur multiple time in the same patient, having two NMS, a high ck plasmatic level, and dealing with its complications leads us more towards the genetic theory.

**Keywords:** Risperidone, high ck levels, acute kidney failure, 2 neuroleptic malignant syndromes, Amisulpride.



## BACKGROUND

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal disease. Initially, the severe forms of NMS were reported in patients treated by first generation antipsychotics compared to those treated with newer antipsychotics. This theory was later abolished.

Though this case presentation, we report the case of a patient who presented a severe form of NMS under two second generation antipsychotics. The first being Risperidone with an extreme level of plasmatic creatine phosphokinase of 50.000 iu/l, shortly after, he developed a second malignant neuroleptic syndrome, immediately after the first intake of Amisulpride, In the literature, those two molecules are normally not reported as frequently responsible of the event.

## CASE PRESENTATION

Mr H, 28 years old, single, no occupation, has been diagnosed with schizophrenia for 5 years now, he's being treated by 6 mg daily of Risperidone since his diagnosis. Two months ago, he was admitted to the medical emergency room for a fever at 39 Celsius (*102.2F*).

The patient's initial check-up revealed, reading his blood-test, it was showing a Natremia at 128mmol/l; kaliemia at 4.8mmol/l; chlorine at 97mmol/l; $HCO^{3-}$ at 14mmol/l; glycemia at 1.36g/l; urea at 3g/l; creatinine at 212mg/l, Creatine kinase (*CK*) at 50,000ui/l, GOT/GPT at 975/297, ferritin at 1836ng/ml and C-Reactive Protein (*CRP*) at 164mg/l. The blood cell count showed platelets at 200.000/µl, WBC at 14,000/µl and Hemoglobin at 12 g/dl then an anemia with Hg at 6g/dl.

Cytobacteriological examination of the urine (*CBUE*) found a urinary infection by *Enterococcus Foecalis* and the abdominopelvic ultrasound was normal. When it comes to the Clinical examination Glascow coma scale (*GCS*) 15/15, temperature:39, Arterial pressure: 14/8 Heart Rate: 100, SaO2 98% with cardiopulmonary examination without abnormalities. In the Intensive care unit (*ICU*) The patient was rehydrated 4L every 24h with discontinuation of Risperidone and 4 sessions of hemodialysis because of his acute kidney failure. Later, the blood-test revealed creatinine at 19mg/l, CPK at 500ui/l and GOT/GPT: 81/35, an amoxicillin-based antibiotic therapy was initiated for 10 days followed with apyrexia and CRP at 45mg/l.

Two months later, after discharge, the patient was referred to the psychiatry department for treatment. the psychiatric interview finds a calm patient, his speech was normal in its course and its continuity, intellectual activities were preserved, he has some thoughts made of a fuzzy mystical delirium badly systematized with hallucinatory mechanism, those thoughts were expressed with a strong affective load "*My JIN says to me that I must leave to the ministry of the religious affairs to know if I am a prophet, my pain is the punishment of god*", his judgment is altered and his insight is negative, the patient was insomniac. his was put on Olanzapine 20mg incrementally and Hydroxyzine 50mg daily. The day his was checked in at the psychiatric department plasmatic CPK level was at 55ui/l.

No clinical improvement was found in the patient with the ongoing treatment six weeks later, Olanzapine was then switched to Amisulpride, after just one take of Amisulpride 50mg, the patient presented a fever at 39 and a hypotension at 8/4, with impaired consciousness and segmental rigidity, associated with tremor, the patient was sent to the medical emergency room where he received a complete check-up and rehydration with constant monitoring, the plasmatic CPK level was 3. 000iu/l. After the management of his second neuroleptic malignant syndrome and after the normalization of CPK. The patient was put on another antipsychotic.

## DISCUSSION

***The uniqueness of our clinical case:***

We can evaluate this case report on two deferent levels, The first episode of NMS had a very high CK level, And the second episode of NMS occurred shortly after switching the drug with the first and after just one dose of Amisulpride.

We should mention that both NMS have been diagnosed using DSM-V diagnostic criteria and Levenson's modified criteria.

Concerning the first episode some elements were difficult to evaluate because the patient was hospitalized in another department of the university hospital (like for example some minor criteria).

NMS occurs in most cases 2 weeks after the treatment is initiated (Addonizio *et al*., 1986) but in same cases in 4-5 hours after initiation of the treatment (Moyes, 1973) which is in line with our study

It is a rare, but life-threatening syndrome associated with the use of dopamine antagonists or the withdraw of dopaminergic drugs. It is described as idiosyncratic medical emergency. Meaning that the reaction depends on the patient; it is not related to the pharmacology of the drug nor dose related (Gurrera *et al*., 2011).

Incidence rates of NMS are 0.01 à 3.2% of patients taking neuroleptic/antipsychotic medications (Caroff & Mann, 1993; Pelonero *et al*., 1998)

The DSM-V criteria for NMS are as follows (APA, 2013):

- Major criteria:
  - ✓ Exposure to a dopamine blocking agent in the last 72 hours
  - ✓ Severe muscle rigidity
  - ✓ Fever

- Minor criteria:
  - ✓ Elevated creatine phosphokinase (ck)
  - ✓ Leukocytosis
  - ✓ Elevated or labile blood pressure
  - ✓ Tachycardia
  - ✓ Altered level of consciousness
  - ✓ Tremor
  - ✓ Mutism
  - ✓ Incontinence
  - ✓ Dysphagia
  - ✓ Diaphoresis

All major criteria are required plus at least 2 minor ones for diagnosing NMS.

***Frequency of SGA-NMS:***

Second-generation antipsychotics (*SGAs*) were originally assumed to be free from the risk of NMS due to their more tolerable pharmacodynamic profile (Tarsy *et al*., 2002); however, subsequently cases of SGA-induced NMS (*SGA-NMS*) began to be reported, the first being Clozapine (Pope *et al*., 1986), then other cases have been reported (Abay & Kose, 2007; Chakraborty & Johnston, 2004).

Some studies suggest that NMS is less common during treatment with atypical antipsychotics than with the classic ones. Indeed, one study estimated the incidence of 2nd generation antipsychotics to be 0.064/ (1,000 x year) (Chen *et al*., 2009). while a meta-analysis indicated that NMS occurred in 0.17-32 people for every 1,000 receiving First Generation Antipsychotics (*FGAs*) (Gurrera *et al*., 2011).

***Are SGA-NMS less severe than others?***

Studies have suggested that NMS due to second generation antipsychotics is less severe compared to conventional neuroleptics, based on lower rates of admission to intensive care (Nakamura *et al*., 2012), and lower mortality rates (Nakamura *et al*., 2012; Trollor *et al*., 2012).

In a case review, eight cases (*5,5%*) of SGA-NMS were fatal, out of a total of 145 cases that reported this information (Belvederi Murri *et al*., 2015). Therefore, the mortality rate appears to be much lower than previous estimates of 10-20% among FGA-NMS cases (Caroff *et al*., 2007; Shalev & Munitz, 1986).

***Ck level as Risk factor:***

Since CK levels are reported to be risk factors of severe MNS and Plasmatic Ck levels are strongly correlated to the intensity of NMS and may be used to track the progress of the syndrome (Shalev & Munitz, 1986) as shown in our case report, the patient presenting a high ck level which results in rhabdomyolysis and kidney failure.

In another metanalysis of case reports and case series focusing on Ck levels and rhabdomyolysis mean ck levels was 15,059 IU/L (Kruijt *et al*., 2020), meaning that our patient is considered to be one of the highest ck reported in literature.

***In our case:***

The second interesting point is the fact that the patient had two MNS in a row which is extremely rare.

We compared the two NMS induced by Risperidone and Amisulpride.

**Table 1: Characterizations of Risperidone and Amisulpride's NMS in our case**

| Characterizations | Risperidone | Amisulpride |
|---|---|---|
| **Major criteria** | Yes | Yes |
| **Minor criteria** | Elevated CPK levels<br>Leukocytosis<br>Tachycardia | Elevated CPK levels<br>altered level of consciousness<br>Tremor<br>Labile blood pressure |
| **Time using AP** | n.r | 1 dose |
| **Normalization within** | n.r | 14 days |
| **Vital prognosis engaged** | Yes | No |
| **CK after resolution** | 45 | 150 |
| **Initial CPK** | 50 000 (250N) | 3200 (16N) |

n.r: not reported in the medical notes

Whereases, A systematic review of case reports regarding those two SGA, described them to be different in presentation (Belvederi Murri *et al*., 2015).

**Table 2: Characterizations of Risperidone and Amisulpride's NMS in the literature**

| | Risperidone | Amisulpride |
|---|---|---|
| **Dose** | 3.7+-3.2 | 480+-179 |
| **Rigidity** | 94.1% | 83.3% |
| **Tachycardia** | 95.7% | 80% |
| **Fever** | 94.3% | 50% |
| **Labile blood pressure** | 73.7% | 83.3% |
| **Tremor** | 91.7 | - |
| **Elevated CK levels** | 97.1% | - |
| **CK levels** | 8500+-1789 | 7950+-6150 |
| **Leukocytosis** | 70.8% | 80% |
| **WBC count** | 15300+-520 | 16600+-4800 |
| **Symptom duration** | 9.7+-9.8 | 10.5+-5.8 |
| **ICU** | 24.3% | - |
| **Recovered** | 87.9% | 80% |

Having two episodes of NMS in a patient is extremely rare, to the best of our knowledge only one case report exists describing a patient having 3 NMS (*Clozapine*, *Amisulpride*, *Risperidone*) (Bottlender *et al*., 2002) having two episodes in one inpatient raises the genetic theory.

Our participant may have a genetic susceptibility to NMS, unfortunately, he did not benefit from genetic profiling due to the lack of logistics.

Indeed, there is some evidence that a variety of genetic alterations (*for example mutations in the debrisoquine 4-hydroxylase* (Kawanishi *et al*., 2000), dopamine D2 receptor genes (Ram *et al*., 1995) or mutation of the Cytochrome P2D6 (*CYP2D6*) gene (Chua *et al*., 2019; Zivković *et al*., 2010) could increase an individual's risk to develop NMS.

## CONCLUSION

Major studies support the fact that neuroleptic malignant syndrome induced by second-generation antipsychotics is characterized by lower incidence, lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics. Which is not the case of our patient, our patient has one of the highest recorded creatinine kinase levels recorded

in our context, with rhabdomyolysis and kidney failure complications needing hemodialysis.

**List of abbreviations**:

**NMS:** Neuroleptic malignant syndrome
**CPK:** Creatine phosphokinase
**CRP:** C-reactive protein
**SGA:** Second generation antipsychotic
**FGA:** First generation antipsychotic
**CYP:** Cytochrome

**Declaration:**

**Ethics approval and consent to participate:** There is no ethical issue.

**Consent for publication:** The patient has given consent for publication

**Competing interest:** The authors declare that they do not have any competing interests.

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**Authors contributions:**

IH was responsible of the patient recruitment, data collection and literature review, MC participated with the literature review and the manuscript writing. SB and AO supervised the research overall and revised the manuscript

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**Availability of data and materials:**

Data sharing in not applicable to this article as no data sets were generated or analyzed during current study.

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