

## Severe long term chronic complications of neuroleptic malignant syndrome: a case report

*Gravi croniche complicanze a lungo termine della sindrome maligna da neurolettici: un caso clinico*

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### Summary

#### Objective

To report a case of neuroleptic malignant syndrome (NMS) in a young woman who survived the acute stage that gradually resolved after 3 months. Afterward she developed a chronic motor disability that was resistant to pharmacological treatment.

#### Case summary

Mrs C.A. is 30-year-old Caucasian woman with mental disability and bipolar disorder type I. In October 2013, she presented with very severe behavioural abnormalities and was treated with intensification of therapy with quetiapine 300 mg TID, haloperidol 4 mg TID, paliperidone 6 mg OD, and fluphenazine decanoate 25 mg i.m. once every 21 days, clonazepam 1 mg OD and lorazepam 2.5 mg OD. In December 2013 extrapyramidal effects developed and hospital admission was necessary. Neuroleptic therapy was immediately stopped. After a few days, fever appeared with consciousness disorders and high levels of creatine kinase. Laboratory tests and imaging studies with negative results were performed. A diagnosis of NMS was

made and she received supportive and specific therapy with dantrolene, diazepam, baclofen, rotigotine and L-Dopa. After 3 months, Mrs. C.A. survived NMS but she showed chronic rigidity and mutism. She was transferred to an intensive neuro-rehabilitation centre.

#### Discussion

The peculiarity of this case is pre-existing central nervous system (CNS) abnormality and atypical symptoms of NMS at presentation. Her mental disability, the use of polypharmacy and long-acting drug likely contributed to the long duration of NMS and its sequelae.

#### Conclusion

In a patient with extrapyramidal symptoms associated with fever and pre-existing CNS abnormalities and mental disability, particular attention must be given to the use of polypharmacy.

#### Key words

Neuroleptic malignant syndrome • Dopamine receptors • Antipsychotics • Mental disability • Rigidity

### Introduction

Neuroleptic malignant syndrome" (NMS) is a rare and potentially fatal complication of the use of neuroleptic drugs<sup>1</sup>. Its incidence is lower than 5 per 1000 persons<sup>2</sup>. NMS derives from the French "syndrome malin des neuroleptiques" and was described by Delay and colleagues, for the first time in 1960, after the introduction of antipsychotics, in association with haloperidol<sup>3</sup>. NMS is characterised by a triad of fever, rigidity and altered mental state<sup>4</sup>. The most popular theory for the development of NMS is blockage of dopamine receptors by antipsychotics to create muscle rigidity that contributes to impaired heat dissipation and hyperthermia<sup>5</sup>. The risk of developing NMS is lower using atypical versus typical antipsychot-

ics, which is based upon their action mechanisms since typical antipsychotics have a higher affinity for dopamine receptors than atypical antipsychotics<sup>6</sup>.

However, the presentation of NMS may be heterogeneous and is reflected in DSM IV criteria<sup>7</sup>. NMS is often difficult to distinguish from other diseases that manifest with extrapyramidal symptoms and from the common side effects of antipsychotic drugs<sup>8</sup> as many conditions can mimic the presentation of the NMS, including heat stroke, CNS infections, toxic encephalopathies and agitated delirium<sup>9</sup>. Several drugs can also cause extrapyramidal symptoms<sup>4</sup>.

The recent NMS literature is controversial. Some authors describe NMS and catatonia as clinical expressions of the same spectrum<sup>10-12</sup>, or consider NMS as a form of malig-

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nant catatonia induced by drugs<sup>13,14</sup>. Catatonic symptoms are described as a residual syndrome after the resolution of NMS<sup>15</sup>, since both catatonia and NMS respond to same treatments. On the other hand, according to other authors catatonia and NMS are two distinct syndromes: NMS is related to dopaminergic dysfunction, and catatonia is related to GABAergic dysfunction<sup>16</sup>. The relationship between catatonia and NMS remains unclear both psychopathologically and pathophysiologically<sup>16</sup>. Differential diagnosis of NMS is of great importance because it is a diagnosis of exclusion<sup>17</sup>. The NMS and its complications such as cardiorespiratory failure, renal failure, aspiration pneumonia and coagulopathies may evolve and can lead to patient death. Rapid diagnosis and intensive treatment are can thus be life-saving. The issue of long-term motor complications has been relatively neglected.

## Case report

Mrs C.A. is a 30-year-old Caucasian woman with mental disability as a sequel of neonatal hypoxia during difficult delivery. Mental disability was confirmed by brain magnetic resonance imaging (MRI) that showed mild cerebral atrophy. Bipolar disorder type I was diagnosed in 2005 and since then her medication included quetiapine 300 mg TID, haloperidol 4 mg TID, clonazepam 1 mg OD, lorazepam 2.5 mg OD and fluphenazine decanoate 25 mg i.m. monthly. In October 2013, she showed an exacerbation of bipolar symptoms with very severe behavioural abnormalities leading to an increased dosage of fluphenazine decanoate (25 mg i.m. once every 21 days) and of the addition of paliperidone (6 mg OD). She was managed through territorial psychiatric services. The psychiatrist had chosen the polypharmacotherapy with oral and a long-acting drug since she had a discontinuous compliance to pharmacological treatment that was related to her mental disability. Despite pharmacological treatment, it was necessary to hospitalise the patient since she continued to show behavioural problems and extrapyramidal symptoms. In December 2013, she was admitted with a flushed and sweaty face. She was unable to speak with sialorrhoea, severe dysphagia, urinary incontinence, tremors and rigidity. Antipsychotic treatment was stopped and supportive therapy with parenteral nutrition and hydration was added. A few days after admission she showed consciousness disorders and a fever from 37–39°C. The other vital parameters were: blood pressure 130/80 mmHg, heart rate 100 beats/min and respiratory rate 26 breaths/min. Physical examination showed consciousness disorders with a Glasgow Coma Scale (GCS) total score of 8, attention deficit, mutism, extreme negativism, inability to eat, generalised rigidity and lack of bowel

control. Her laboratory values were: WBC  $7.11 \times 10^9/l$ , RBC  $4.84 \times 10^{12}/l$ , Hb 14.2 g/dl, platelets  $226 \times 10^9/l$ , MB 193 ng/ml, CPK 1131 IU/L, potassium 2.9 mEq/l and pH 7.383. At the time of admission, initial differential diagnoses included head stroke, viral and bacterial infections, metabolic disorder and central nervous system degenerative diseases. Accordingly, she was submitted to laboratory tests and imaging studies. Head computed tomography Scan (CT) and MRI with contrast medium, chest X-ray, urine analysis, blood cultures, electroencephalogram and examination of the cerebro-spinal fluid showed no abnormalities. According to the DSM IV<sup>6</sup>, she met the criteria for NMS.

The patient was treated in the psychiatry unit with supportive therapy for vital functions and specific therapy. Supportive therapy included: hydration, electrolyte restoration, oxygen and blood pressure aids and parenteral nutrition together with antipyretic (i.e. paracetamol), antibiotics (i.e., cephalosporins, fluoroquinolones) and anticoagulant treatment (i.e., fraxiparin) to reduce the risk of infectious or thrombotic complications caused by immobility. The specific treatment included dantrolene (1 mg/kg) and diazepam (10 mg TID) intravenous, but no benefits were seen in the first 20 days (WBC  $3.31 \times 10^9/l$ , RBC  $4.28 \times 10^{12}/l$ , Hb 11.8 g/dl, platelets  $209 \times 10^9/l$ , MB 343 ng/ml, CPK 562 IU/L, potassium 3.0 mEq/l). Accordingly, rotigotine 6 mg/24h patch therapy was added. After 15 days she began to swallow, but the rigidity, fever and mutism did not improve (WBC  $4.27 \times 10^9/l$ , RBC  $3.83 \times 10^{12}/l$ , Hb 10.7 g/dl, platelets  $218 \times 10^9/l$ , MB 225 ng/ml, CPK 287 IU/L, potassium 3.4 mEq/L). At 30 days after the addition of baclofen (25 mg TID) and levodopa/benserazide (200/50 mg TID) body temperature and blood values returned to normal (WBC  $3.32 \times 10^9/l$ , RBC  $4.29 \times 10^{12}/l$ , Hb 11.3 g/dl, platelets  $236 \times 10^9/l$ , MB 85 ng/ml, CPK 152 IU/L, potassium 4.1 mEq/L and pH 7.48). The patient began to eat independently with improvement in consciousness disturbances (GCS 12). Rigidity and mutism was unchanged. On February 2014, the patient was transferred to an intensive neuro-rehabilitation centre. She started passive mobilisation and exercises for standing, with only minimal improvement in lower limb activity and mild worsening of upper limb motor activity. After 6 months, the patient returned to her home, motor symptoms decreased slightly and she patient was able to walk supported by walker. She was able to eat and perform autonomous functions, although dysarthric elocution with very short sentences remained.

## Discussion

The atypical case presentation is due to chronic motor symptoms, such as rigidity even after resolution of fever.

In the most cases patients recover in a few weeks and survive without sequelae; the duration of NMS episodes may be prolonged when long-acting depot antipsychotics are implicated<sup>4</sup>. Patients may sometimes remain with cognitive deficits and motor abnormalities, including rigidity, tremor and dystonic contractures<sup>17</sup>. Some cases of NMS after administration of typical and atypical antipsychotics have been described<sup>6 19 20</sup>. The use of polypharmacy is still controversial: some authors think that these medications are more effective, while others assume that they cause onset of extrapyramidal symptoms or NMS more frequently<sup>19</sup>. In this case, polypharmacy does not allow making a connection between a specific drug and the development of NMS.

The patient's mental disability related to neonatal hypoxia with cerebral atrophy is another factor that could interact with drug treatment to determine her neurological outcome. In fact, preexisting CNS abnormalities have been described as risk factors for NMS<sup>21</sup> and CNS damage is a risk factor to develop persistent sequelae<sup>22</sup>.

The muscle relaxants dantrolene and diazepam, which contrast muscle rigidity caused by antipsychotics, were not sufficient to resolve the NMS, and it was necessary to add a dopamine agonist drug such as rotigotine<sup>23</sup> which is a non-ergot dopamine agonist suitable for 24 hour transdermal delivery patches. With L-Dopa the extrapyramidal symptoms were controlled, although there was little improvement. The choice to not use bromocriptine or amantadine was made because the patient could not swallow, and thus rotigotine patches were considered a good alternative. When swallowing function was restored, L-Dopa was added.

The delay in the start of treatment may have been another cause of long duration of rigidity and mutism. In fact, the morbidity and associated with NMS can be decreased with early recognition, early discontinuation of neuroleptics and aggressive treatment<sup>25</sup>; in the present case, intravenous treatment of NMS with dantrolene and diazepam was started 10 days after laboratory tests and instrumental exams were negative. Furthermore, the rigidity, mutism and contractures of the limbs may also be explained by a residual catatonic parkinsonian state<sup>26</sup>.

## Conclusion

The peculiarity of this case with pre-existing CNS abnormalities and the atypical NMS symptoms made diagnosis difficult; polypharmacy with typical and atypical neuroleptics together with the use of long-acting drug may be possible causes of the long duration of NMS and its sequelae.

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