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Case Report

Neuroleptic malignant syndrome: Possible relationship between neuroleptic treatment and smoking cessation

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ABSTRACT – We report the case of M., a schizophrenic patient who was treated with high doses of antipsychotics for a long time allowing him to be stable for years. He then decided to give up smoking and two weeks later he suffered a syndrome diagnosed as Neuroleptic Malignant Syndrome with somatic complications. This caused his death two months after the start of the symptoms. We discuss the implications of smoking cessation in the origin of the syndrome due to a lower metabolism of psychotropic medications, which previously had been well tolerated. We conclude that it is important to take into account the smoking and caffeine intake of these patients, as well as other metabolic inductor or inhibitor drugs.

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Introduction

Neuroleptic malignant syndrome (NMS) is a rare, unpredictable, and potentially lethal disease that results from the adverse side effects of antipsychotic medication. Currently, there is no satisfactory treatment avail-

able. Modern therapy is halting neuroleptic and anticholinergic treatment, vital support, and medical treatment with bromocriptine, dantrolene, amantadine, benzodiazepines or L-Dopa^{1,2,3}. Some studies suggest that Electroconvulsive therapy (ECT) can be effective in severe, or treatment resistant, NMS. A response to ECT usually appears after a

mean of six sessions^{4,5} although this is unpredictable.

Clinical case

We present the case of M., 38 years old, diagnosed with paranoid schizophrenia beginning at 17 years old. He had several psychiatric hospitalizations, during the nine years prior to the actual episode. Over the last two years, this patient, who received a consistent psychotropic treatment which included: risperidone 3 mg/day, injectable risperidone 100 mg/15 days, olanzapine 10 mg/day, topiramate 600 mg/day and lithium carbonate 800 mg/day, was clinically stable. He previously smoked 80 cigarettes / day but two weeks before he was admitted at hospital he had stopped. He had no additional pathologic antecedents. Previous analyses were performed to control lithium treatment, with lithemias between 1 (two years before this episode) and 0.7 mEq/l (level three months before and at the emergency room), being the rest of biochemical and blood analyses in the normal range. Another drug and creatine phosphokinase levels were not solicited before hospital admission.

M. was admitted to the emergency room with a fever and complaints of not feeling well. As his condition worsened in few hours he became comatose (Glasgow 6), without neurological focalized deficit and was in a hypotonic state after sedation; stiffness was not evaluated when he arrived to emergency room, and muscular tone was only considered when the patient was in coma. Other symptoms were sweating, dyspnoea, tachypnoea, tachycardia, and a body temperature of 42.3°C. He was subsequently admitted to the ICU. His condition was

apparently induced by working in a moderately hot environment (30-32°C).

In the ICU, where he was admitted with a Glasgow 2, blood analysis, EEG, cranial CAT and MRI scan, and lumbar puncture were performed; viral, neurodegenerative, epileptic status, cerebral vasculopathy and autoimmune illnesses were ruled out. The only altered parameters were low level plasma platelets and high CPK (4026 U/l) levels. Levels of CPK were not analysed before emergency room admission. During the first week his level of consciousness slightly improved, but he was still confused, requiring high doses of sedation.

Among the differential diagnoses, heat stroke and neuroleptic malignant syndrome (NMS) were most probable. Topiramate can be a predisposing factor of heat stroke due to reduced transpiration and inhibition of carbonic anhydrase⁶, while lithium carbonate treatment is a risk factor to develop a NMS⁷. One major sign of NMS, rigidity, was not apparent in this patient probably due to sedation. However, two other major criteria (hyperthermia, augmentation of CPK) and more than three minor criteria (tachycardia, tachypnoea, alteration of consciousness) of NMS were present. The patient did not respond to the usual heat stroke treatment. He was then treated with electrical convulsive therapy. After ten sessions (parameters: 1.4 msec, 800 mA, 1.5 seg, and 90 Hz, three sessions per week) the patient's neurological state did not improve and treatment was discontinued.

During ICU hospitalization, the patient's physical state was complicated by a left lung infection due to atelectasia with hypoxemia. Even after hyperthermia, renal function, liver function, and platelet levels returned to normal values. Neurological damage persisted, with oscillations of con-

sciousness and collaboration. During hospitalization, an axonal polyneuropathy developed in the patient with a flaccid paraparesia.

He was discharged of ICU with normalization of vital signs, but the polyneuropathy persisted and he could not speak well due to the prolonged intubation, his consciousness was fluctuating, though no psychotic symptoms were observed. Two months after discharge from the ICU, during his hospital stay the patient suffered a psychotic episode and was treated with benzodiazepines and olanzapine. After this treatment he presented with pneumonia and two weeks later he died in the ICU from complications of the pneumonia and polyneuropathy.

Discussion

The pathogenesis of NMS is unknown but may be due to a blockage of dopaminergic receptors in hypothalamus (alterations of thermoregulation and vegetative nervous system) and in nigrostriatal track (parkinsonism like rigidity and tremor). Other neurotransmitters like GABA, adrenaline, serotonin, and acetylcholine appear to be related to this syndrome directly or indirectly^{1,2,8}. Although NMS is an idiosyncratic reaction; it more likely occurs with neuroleptics that have a strong effect upon the D2 receptor (like haloperidol) than with neuroleptics that have minor antipsychotic powers.

If rigidity and hyperthermia are absent the diagnosis is questionable, but NMS with minor hyperthermia and rigidity are described as being related to atypical antipsychotic drugs⁸⁻¹³. NMS must be considered in the differential diagnosis of every patient receiving neuroleptic treatment who presents a fever of unknown origin with or

without muscular rigidity¹⁴. Biochemical alterations present in NMS are not specific, it is frequent the presence of leukocytosis, CPK augmentation, hydroelectrolyte alteration (hyperkalemia, metabolic acidosis, and hypocalcaemia), and moderate increases in hepatic transaminases; they are not useful for diagnosis but may be used to evaluate severity of syndrome^{1,3,15-17}.

Patients with schizophrenia are more likely to have a higher rate of nicotine use and more likely to smoke high-tar cigarettes than the general population or patients with other psychiatric diagnosis¹⁸⁻²⁰. Tobacco smoking seems to act upon cytochrome CYP1A2, inducing neuroleptic metabolism, mainly on clozapine and olanzapine, and polymorphisms within the variation in the cytochrome P450, frequent for isoenzyme 1A2, may influence drug-induced adverse effects and drug efficacy²¹. Several studies suggest that smokers need higher levels of antipsychotics than non-smokers²²⁻²⁴. Smoking can lower the blood levels of some antipsychotics by as much as 50%. Neuroleptic toxicity can appear two-to-four weeks after smoking cessation²². This effect may be related to the lack of metabolic induction by smoking²³. In addition, this effect may be less important upon metabolism of risperidone and aripiprazole (CYP2D6 (nicotine could compete with risperidone because the two of them are metabolised with this isoenzyme) and CYP3A, quetiapine (CYP3A) and ziprasidone (CYP3A and an aldehyde oxidase). On the other hand, caffeine is metabolized by CYP1A2 like neuroleptics and changes in its intake can change the plasma concentration of the drug because of enzyme competition²³.

Nicotine increases mesolimbocortical dopaminergic activity in the nucleus accumbens and the prefrontal cortex^{25,26}. This dopamine stimulation could explain its use as a form of self-medication to reduce nega-

tive, cognitive and affective symptoms and could explain the strong smoking habit of schizophrenic patients²⁵⁻²⁸, though this effect has not been replicated in consistent studies. And smoking quitting has not been shown to worsen the disability in schizophrenia²⁶. In some studies the smoking group of schizophrenia patients demonstrates less akathisia, but not in all of them^{25,28,29}. In patients with schizophrenia, smoking cessation is more likely to bring about problems, than compared with the general population.

Conclusions

In this patient, the NMS could have resulted from both physical and metabolic factors. The physical factors could have included working in a warm place in summer, physical exercise, and reduced sweating because of topiramate treatment. The main metabolic confounding factor was the slow-down of neuroleptic elimination, mainly olanzapine, because the lack of enzymatic induction due to recent smoking cessation. Other factors that could contribute to the development of the syndrome were topiramate treatment associated with neuroleptics, which increases the danger of heat stroke if hypothalamus deregulation occurs, extended treatment with high doses of neuroleptics, and smoking cessation that could have aggravated previously stable plasma drug levels.

In patients receiving several treatments that result in complex metabolic profile, adding the adverse effects and mechanisms of external agents like salt, smoking, or caffeine intake can alter neuroleptic plasma levels leading to potentially lethal adverse effects. This must be considered when a patient decides to change some habits or

received another drug and drug levels should be performed.

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